

Diabetes und Adipositas

Ansätze der medizinischen und pharmazeutischen Forschung

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Innovationen in der Medizin und in der Pharmazeutischen Forschung lösen

“unmet medical needs”

(ungelöste medizinische Bedürfnisse)

Innovationen in der Medizin lösen “unmet medical needs”

Die Ziele in der Medizin:

Die **Vermeidung** (*Prävention*) , **Heilung** (*kurativ*) oder **Therapie** von Erkrankungen

Therapien sollen

- ▶ wirksam und sicher
- ▶ wenig belastend sein,
- ▶ Komplikationen vermeiden,
- ▶ Lebensqualität erhalten und
- ▶ normale Lebenszeit ermöglichen

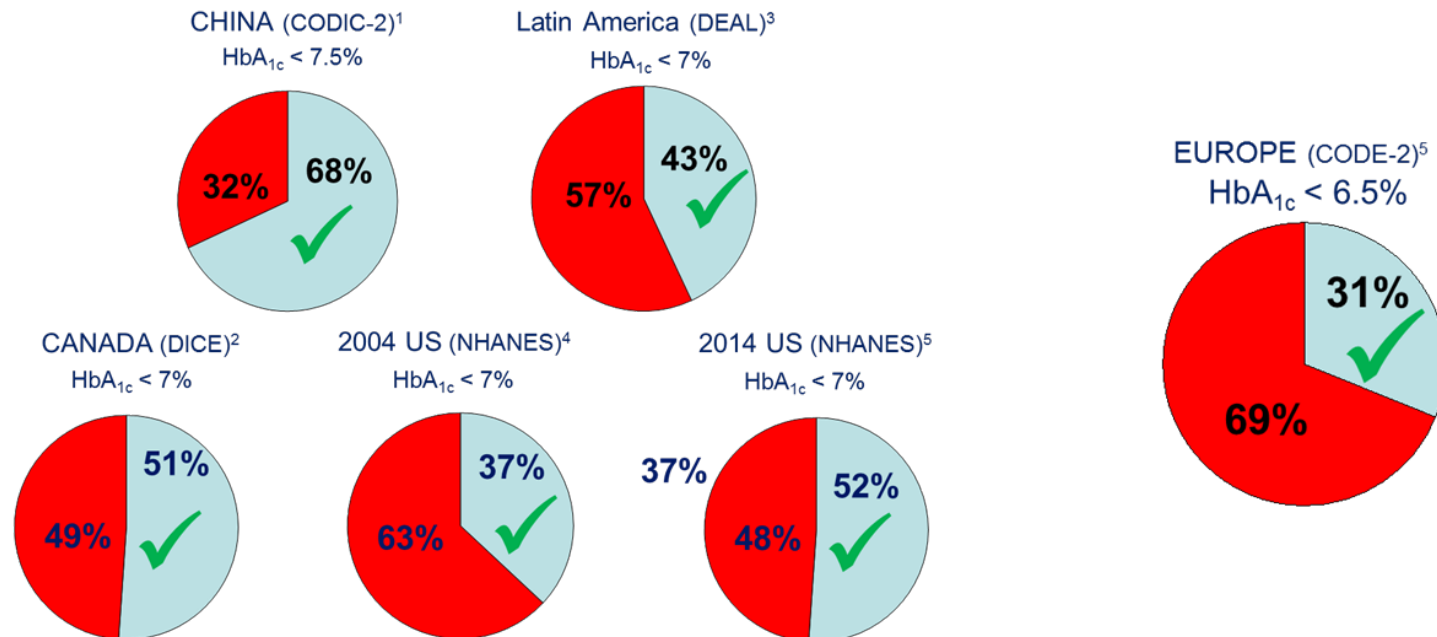


Innovationen in der **Diabetestherapie** lösen “unmet medical needs”

Diabetestherapie soll

- ▶ wirksam und sicher,
 - ▶ wenig belastend sein,
 - ▶ Akut- und Spätkomplikationen vermeiden,
 - ▶ Lebensqualität erhalten
 - ▶ normale Lebenszeit ermöglichen
- = BZ (HbA1c) normalisieren ohne Hypoglykämien, Gewicht reduzieren
 - = einfache Gabe z.B. einmal täglich – einmal wöchentlich – oral vs sc.
 - = Gefäßschäden, Hirnleistung, vorzeitiges altern
 - = wenig Nebenwirkungen, wenig Aufwand im Alltag
 - = Verbesserung “harter Endpunkte”, z.B. Riskoreduktion CV Mortalität

Ungelöste medizinische Bedürfnisse in der Diabetologie – Wirksamkeit der Therapie HbA1c



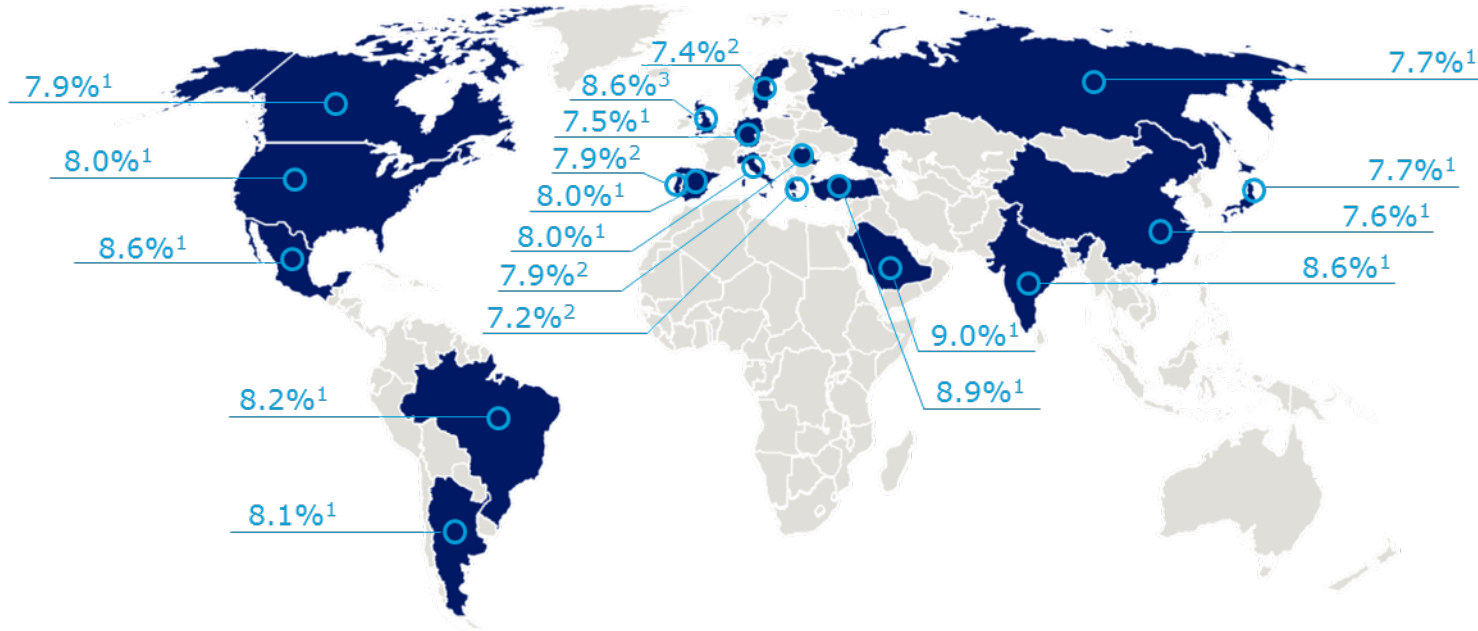
¹Xingbao C. *Chinese Health Economics* 2003; Ling T. *China Diabetic Journal* 2003.

²Harris SB, et al. *Diabetes Res Clin Pract* 2005; 70:90–97. ³Lopez Stewart G, et al. *Rev Panam Salud Publica* 2007; 22:12–20.

⁴Saydah SH, et al. *JAMA* 2004; 291:335–342. ⁵Liebl A, et al. *Diabetologia* 2002; 45:S23–S28. 5. NHANES 2014

Ungelöste medizinische Bedürfnisse in der Diabetologie – **Wirksamkeit der Therapie HbA_{1c}**

Mittlerer HbA_{1c} (%) für mit Insulin behandelte Patienten mit Typ 2 Diabetes



¹Polinski et al. *BMC Endocr Disord* 2015;15:46 (including supplement);

²Oguz et al. *Curr Med Res Opin* 2013;29:911–20;

³Blak et al. *Diab Med* 2012;29:e13–20;

Ungelöste medizinische Bedürfnisse in der Diabetologie – QoL und Sicherheit

Diabetes medication and daily life



39%

of people with diabetes said that their diabetes medication routine interfered with the ability to live a normal life

Worry about hypoglycaemia



56%

of people with diabetes felt very worried about the risk of hypoglycaemia

Ungelöste medizinische Bedürfnisse in der Diabetologie - **Patientensicht** *n= 3000, US, 2016*

Key Points

- Few people with diabetes surveyed feel “very successful” on current therapies, regardless of the metric: glucose, complications, emotional well-being, burden of care, social life.
- Time-in-range has the biggest impact on daily life with type 1 and 2 diabetes. It is a shared - and unmet - need.
- Current therapies have significant room to improve on time-in-range.
- Patients are very interested in greater FDA focus on time-in-range and quality of life.

Patient Priorities for Diabetes Drugs: What Does Success Look Like?

A download on 3,000+ patient views collected in August 2016

Kelly L. Close

Founder and Chair
The diaTribe Foundation

Richard Wood

Founder and CEO
dQ&A

FDA Workshop: “Outcomes Measures for New Diabetes Therapies Beyond A1c”
Silver Spring, MD
August 29, 2016

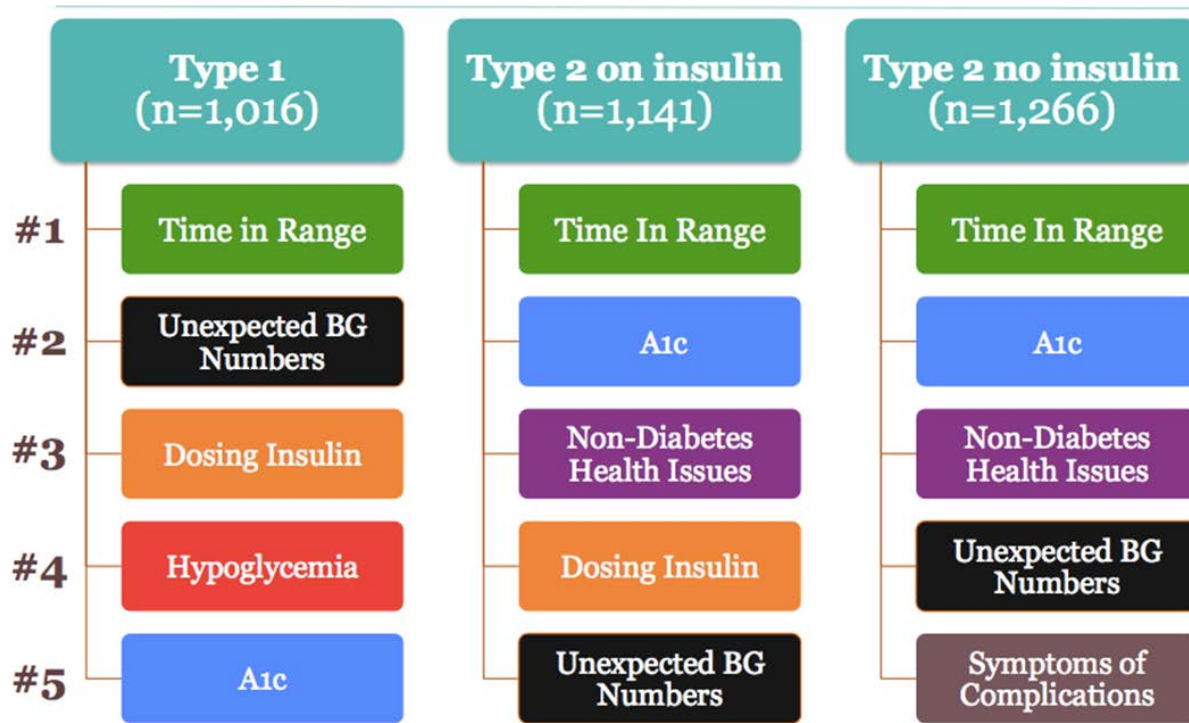
diaTribe
dQ&A

Slide 1

dQ&A

diaTribe Slide 2
HUMAN HUMAN

Ungelöste medizinische Bedürfnisse in der Diabetologie - **Patientensicht** *n= 3000, US, 2016*

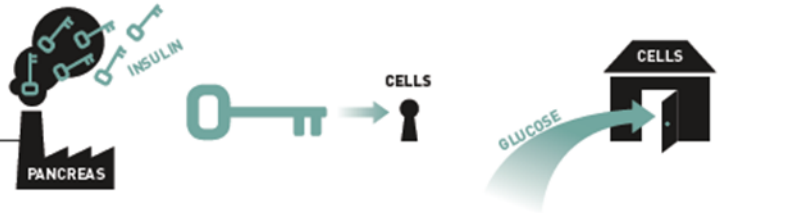


Innovationen in der Behandlung des Diabetes Mellitus

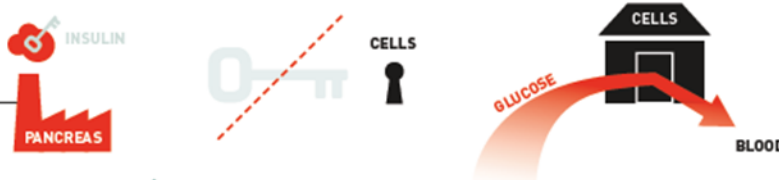


Was ist Diabetes ?

Normal situation



Typ 1 Diabetes



lebenslange **Insulin**
(-ersatz) **therapie**

Typ 2 Diabetes

gestational diabetes



**Lebensstiländerung +
medikamentöse Therapie
(auch Insulin) mit
unterschiedlichen
Ansätzen**

Typ 1 Diabetes ... was passiert ohne Therapie ?

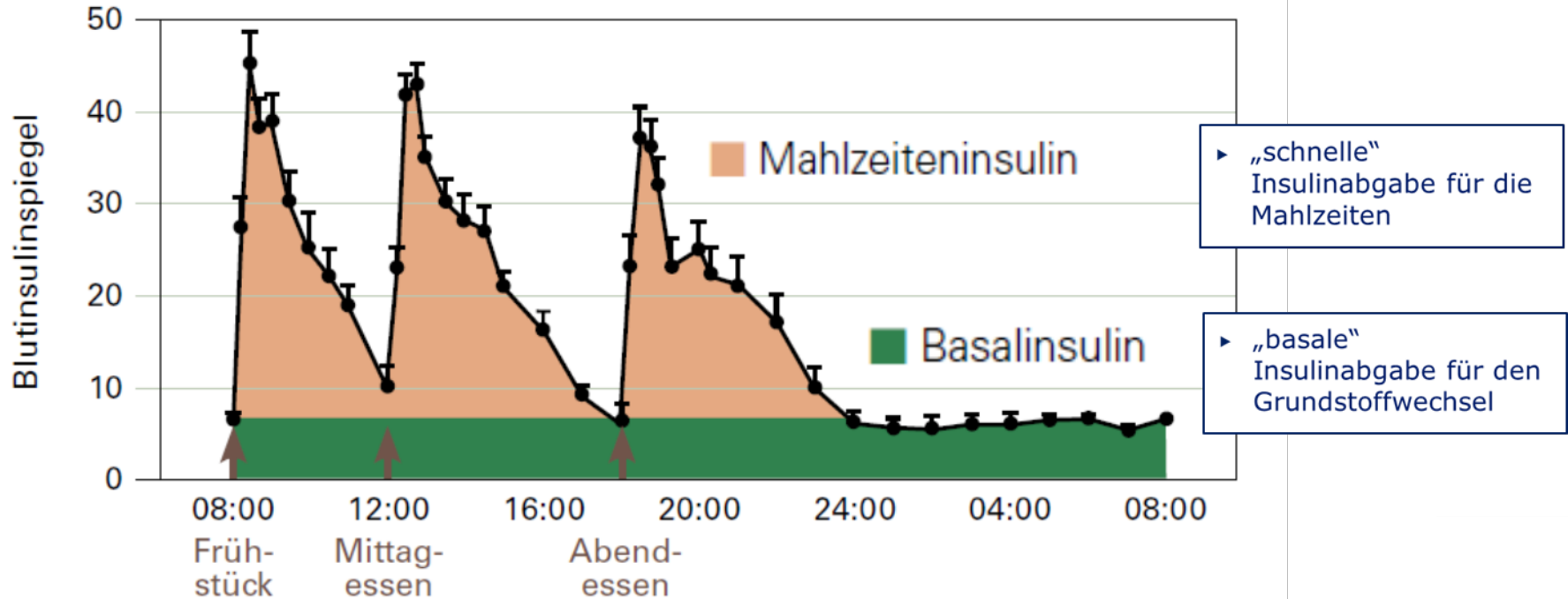


- ▶ Kein Glukosetransport in Körperzellen
- ▶ Energiegewinnung durch Aufbrauch von Fett und Protein (auch Organ- und Strukturprotein)
- ▶ Kachexie und früher Tod

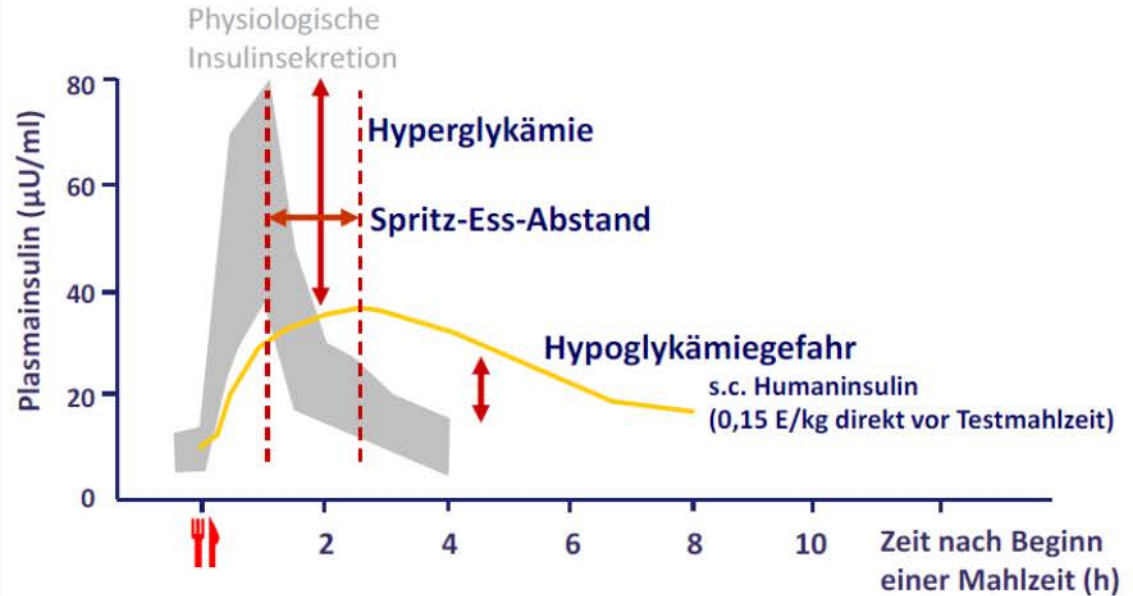
- ▶ **Lebenslange Insulin (-ersatz) therapie nötig**

Physiologie der Insulinabgabe durch die Bauchspeicheldrüse:

Sehr schnell für Nahrungsglukose, lang für Grundstoffwechsel



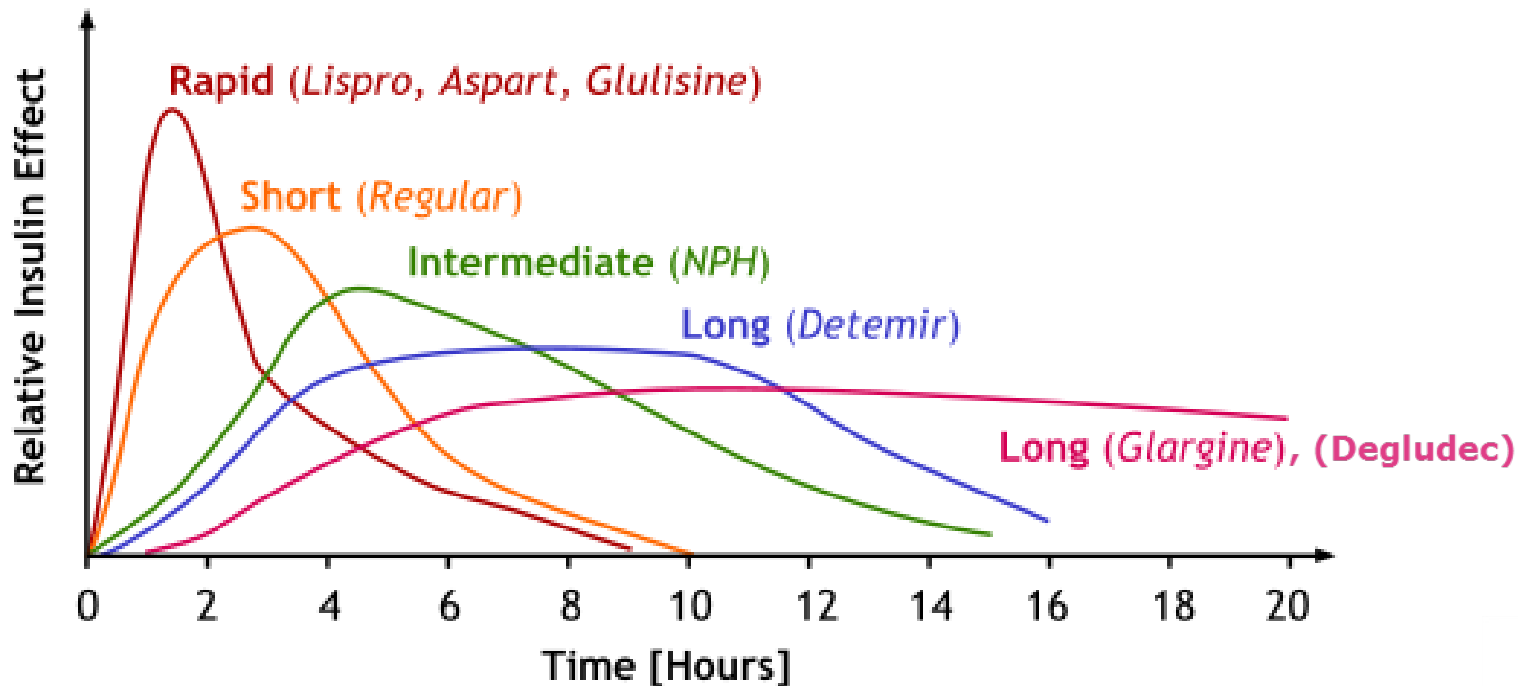
Injektion von Humaninsulin subkutan



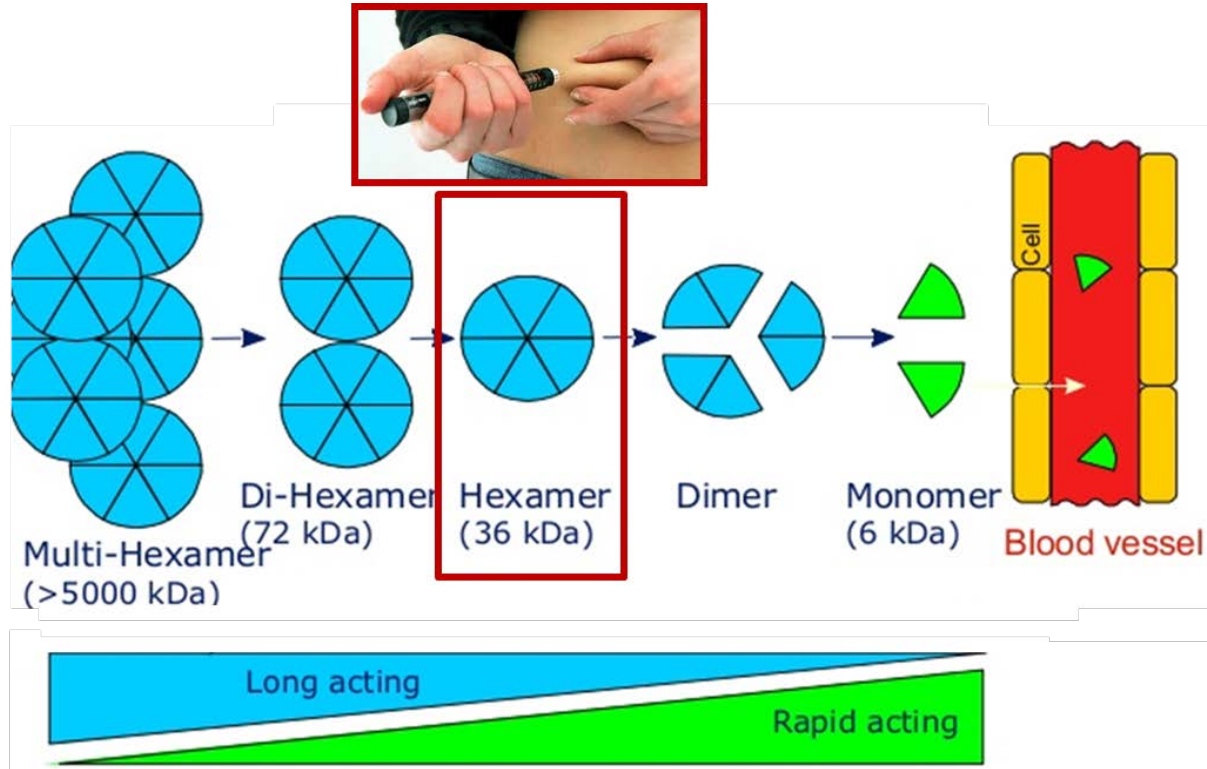
Herausforderung für die Insulinentwicklung:

Insuline für die Mahlzeiten = (sehr) schnell wirksam

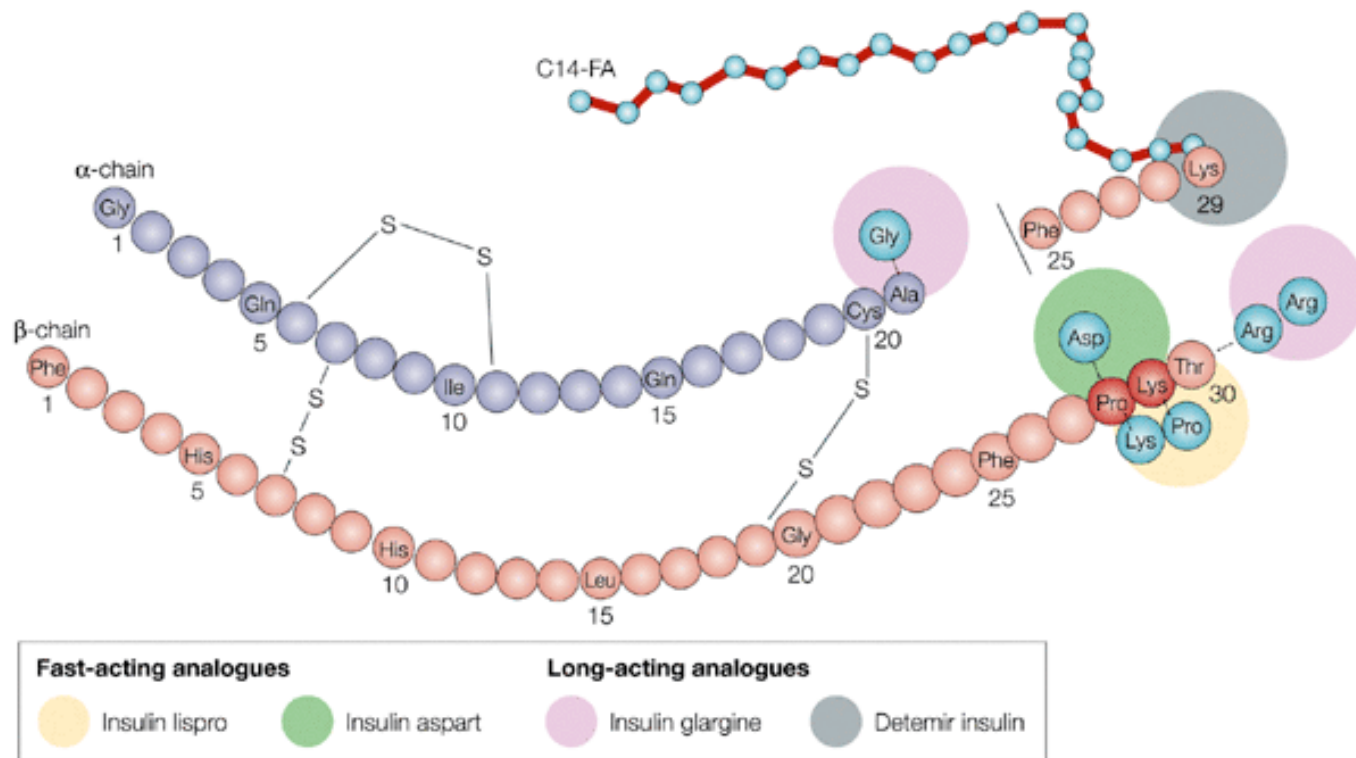
Insuline für den Grundstoffwechsel = lang (und gleichmäßig) wirksam



Wie entstehen Insuline mit unterschiedlichen Eigenschaften ?

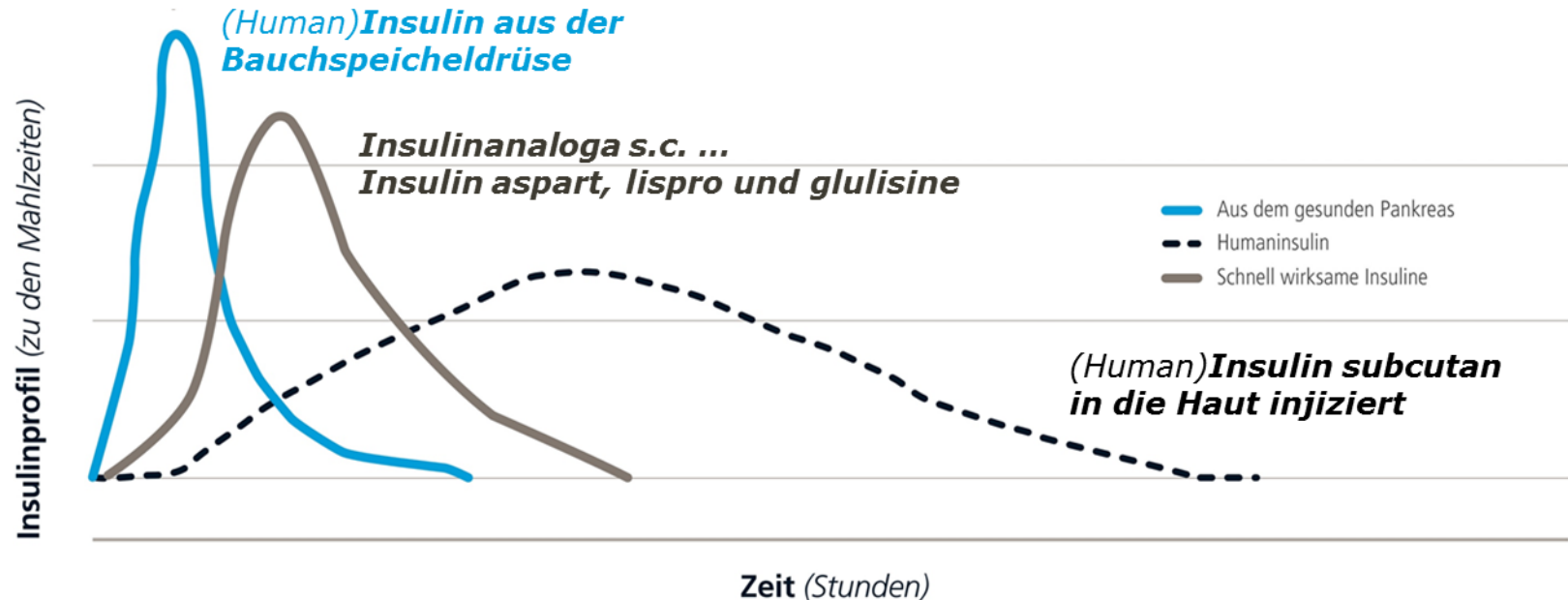


Wie entstehen Insuline mit unterschiedlichen Eigenschaften ?



Mahlzeiteninsulin = schnell wirksame Insuline

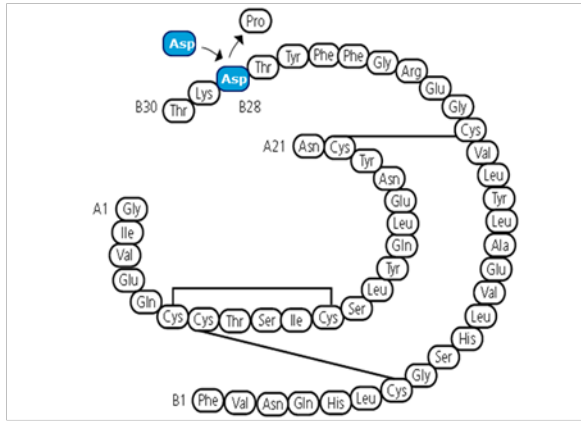
Schnelle Insulinverfügbarkeit ist wichtig für niedrige Blutzuckerspiegel nach den Mahlzeiten und Flexibilität des Injektionszeitpunktes



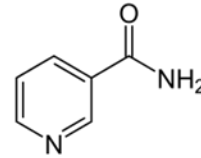
Nächste Generation schneller wirksamer Insuline

Faster-acting insulin aspart durch Zusätze aus der "GRAS Liste" zu der pharmakologischen Formulierung von Insulin aspart

Insulin aspart

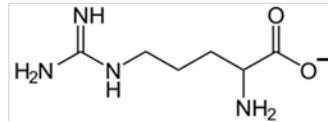


**Niacinamid = Vitamin B3:
Resorptionsmodifikator**



Verantwortlich für die schnelle Resorption

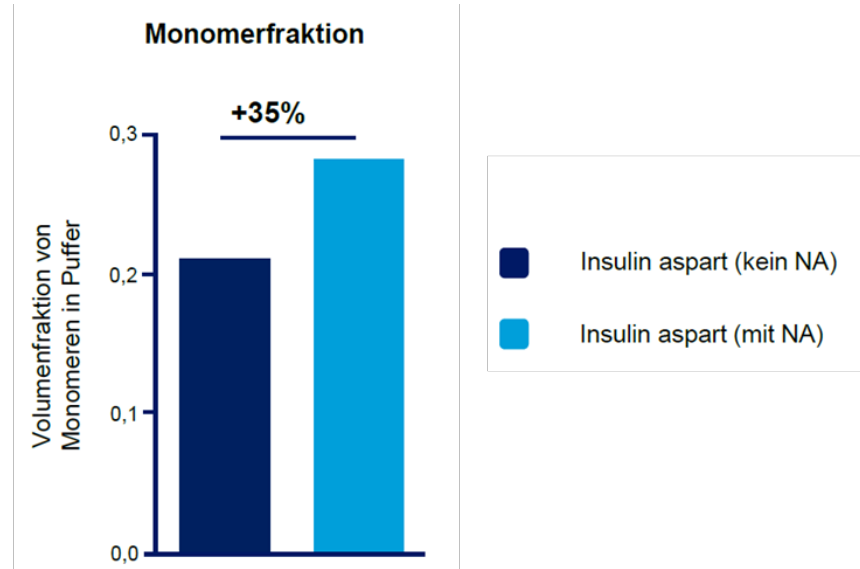
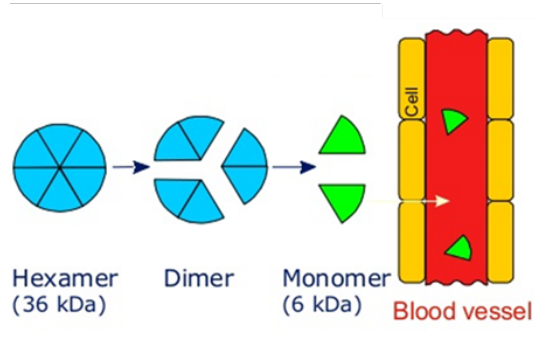
Arginin: Stabilitätsverbesserer



Verbessert die Stabilität des Insulins

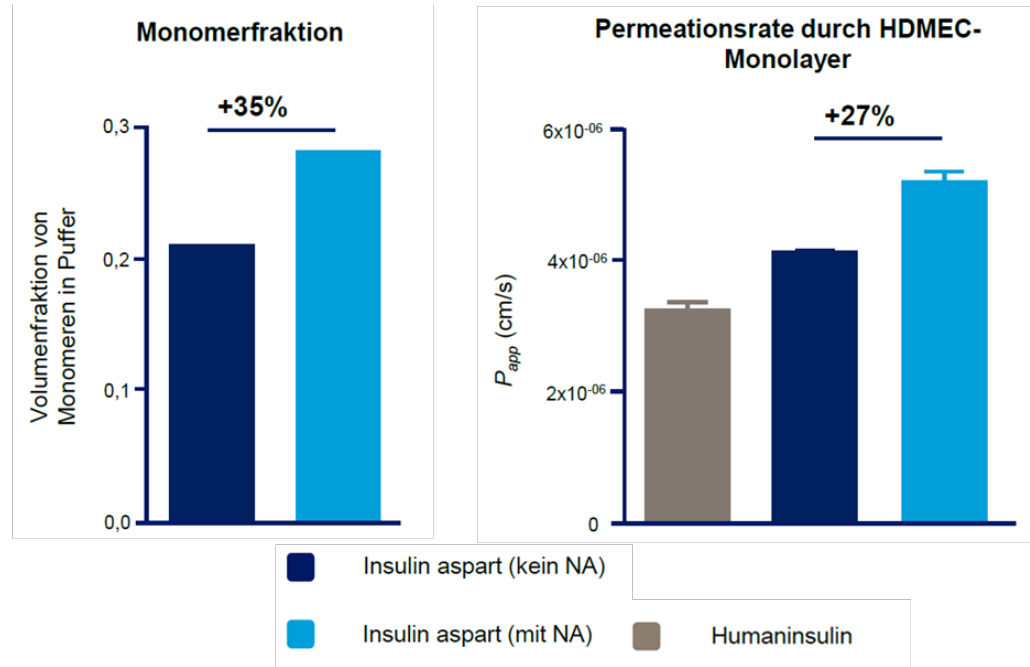
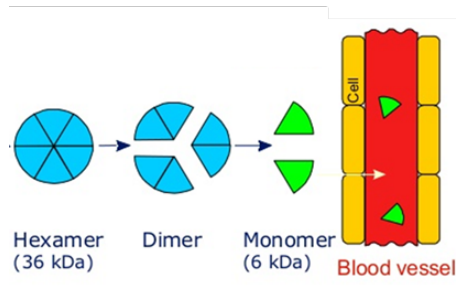
Faster-acting Insulin aspart

Niacinamid (Vitamin B3) begünstigt die Monomersituation (+35%) und damit eine sehr schnelle Absorption in die Blutbahn



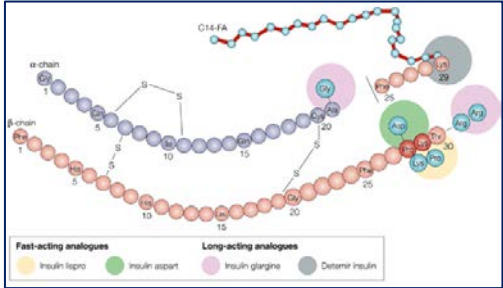
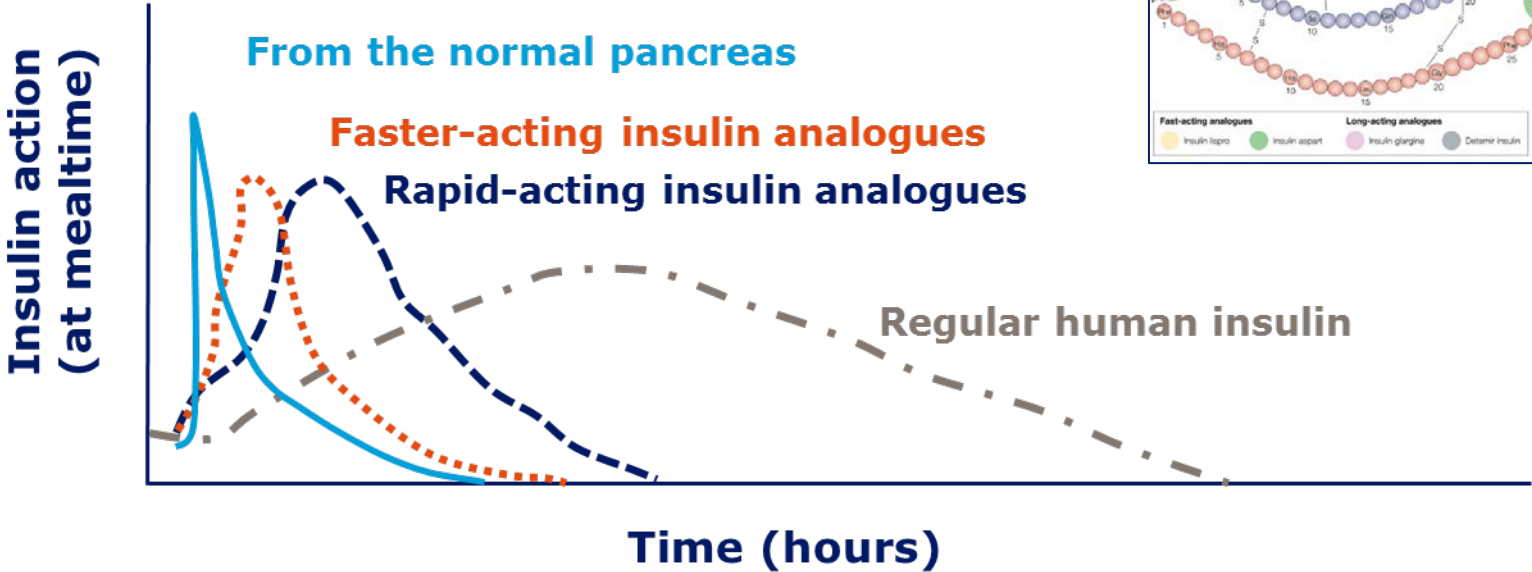
Faster-acting Insulin aspart

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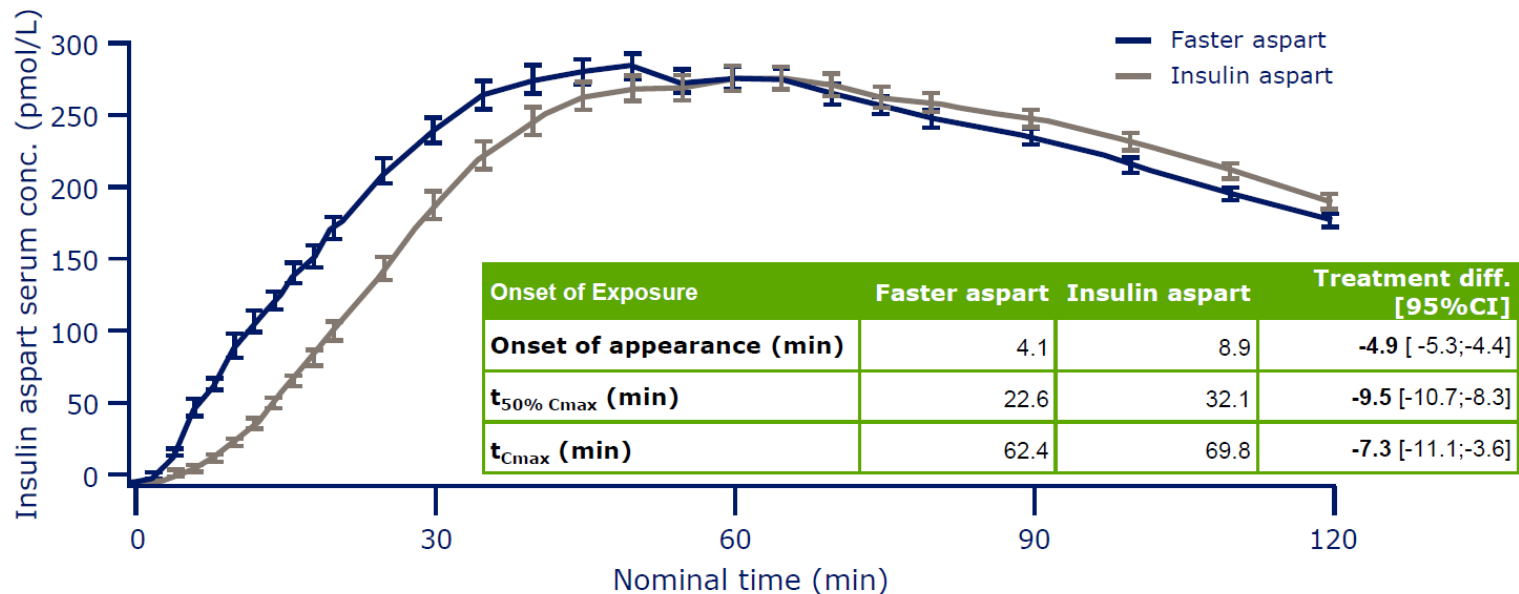
Nächste Generation schnell wirksamer Insuline

Faster-acting Insulin aspart



Faster-acting Insulin aspart

Doppelt so schnelles Auftreten im Blut, doppelt so hohe Insulinexposition und etwa 74% höhere Insulinwirkung in den ersten 30min in Clamp Versuchen



Adults with T1DM, dose 0.2 U/kg, trials 3887, 3888, 3889, 3891, 3921, 3978, n=261 (faster aspart), n=256 (aspart)
Heise T et al. Diabetes 2016; 65 (Suppl. 1):929-P

Faster-acting Insulin aspart

Klinische Wirksamkeit in T1DM – Onset-1 Studie: Niedrigere Blutzuckerspiegel nach den Mahlzeiten und niedrigere HbA1c -Werte

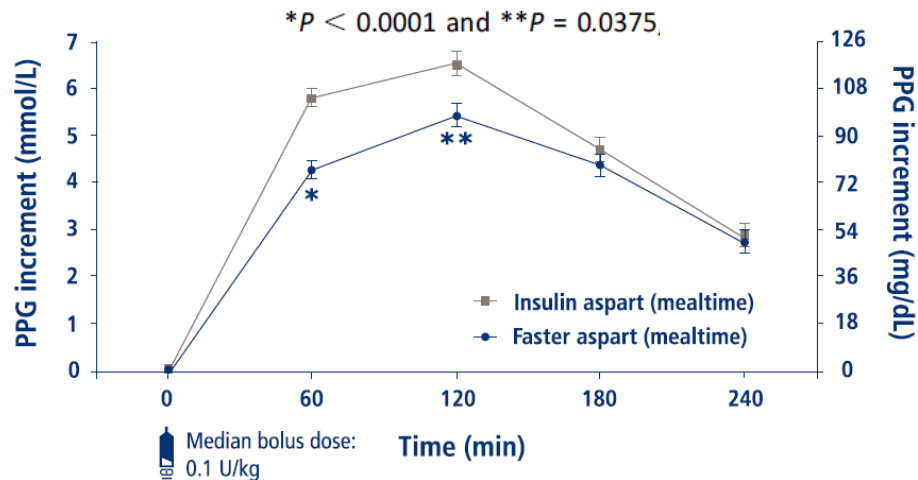
Diabetes Care



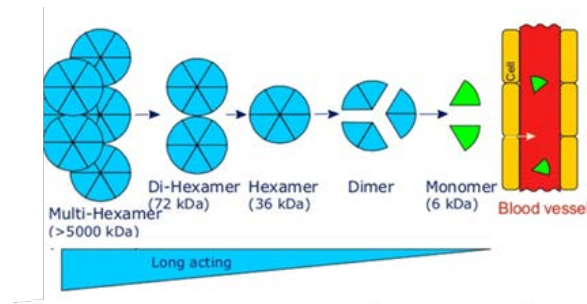
Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (Onset 1)

DOI: 10.2337/dc16-1771

David Russell-Jones,¹ Bruce W. Bode,²
Christophe De Block,³ Edward Franek,⁴
Simon R. Heller,⁵ Chantal Mathieu,⁶
Athena Phillis-Tsimikas,⁷ Ludger Rose,⁸
Vincent C. Woo,⁹ Anne Birk Østerskov,¹⁰
Tina Graungaard,¹⁰ and
Richard M. Bergenstal¹¹



Basalinsuline ... für den Grundstoffwechsel



λ	Half life (hours):	5-10	12-19	25
	Variability:	High	Medium	Low

Basalinsuline ... für den Grundstoffwechsel

Insulinmolekül	Handelsname	Halbwertszeit (Stunden)	Wirkdauer (Stunden)	intraindividuelle Wirkvariabilität (CV% of AUC _{GIR})
NPH-Insulin	Huminsulin Basal [®] Insuman Basal [®] Protaphane [®] Berlinsulin H Basal [®]	5–10	13–16	68
Insulin detemir	Levemir [®]	5–7	16–23	27
Insulin degludec *	Tresiba [®]	ca. 25	>42	20
Insulin glargin U100	Lantus [®] Abasaglar [®]	7–13	21–27	48
Insulin glargin U300	Toujeo [®]	18–19	ca. 36	34

Basalinsuline NPH Insulin vs. Insulin glargine (100IU/ml)

The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

MATTHEW C. RIDDLE, MD¹
JULIO ROSENSTOCK, MD²
JOHN GERICH, MD³

ON BEHALF OF THE INSULIN GLARGINE 4002
STUDY INVESTIGATORS*

DIABETES CARE, VOLUME 26, NUMBER 11, NOVEMBER 2003

Reviews/Commentaries/ADA Statements

META - ANALYSIS

Reduced Hypoglycemia Risk With Insulin Glargine

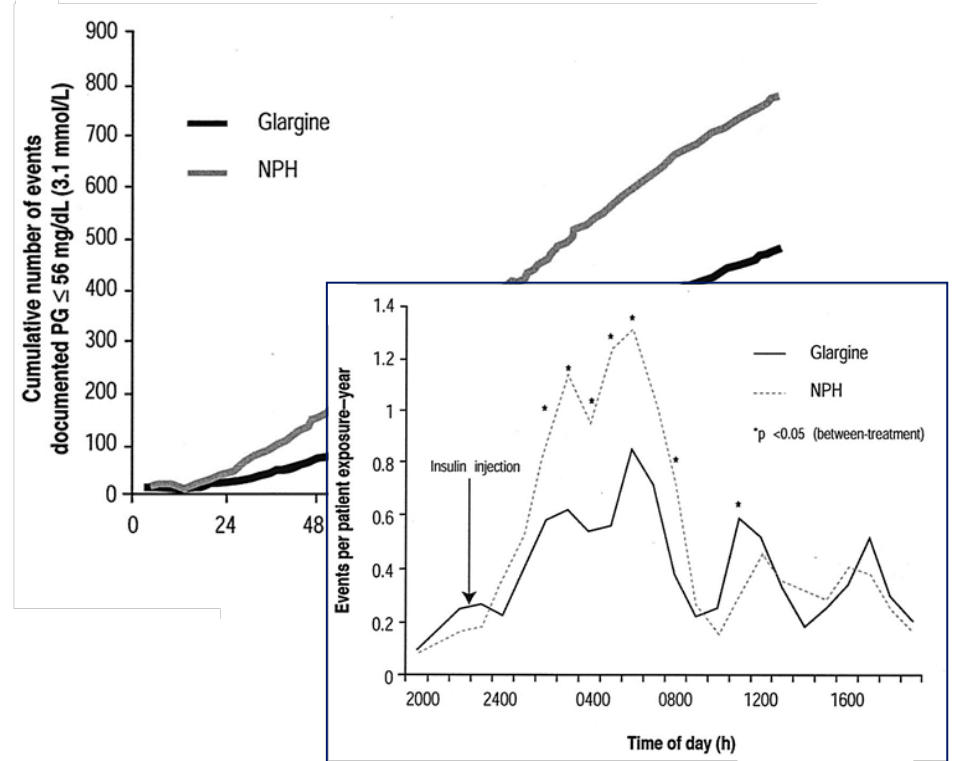
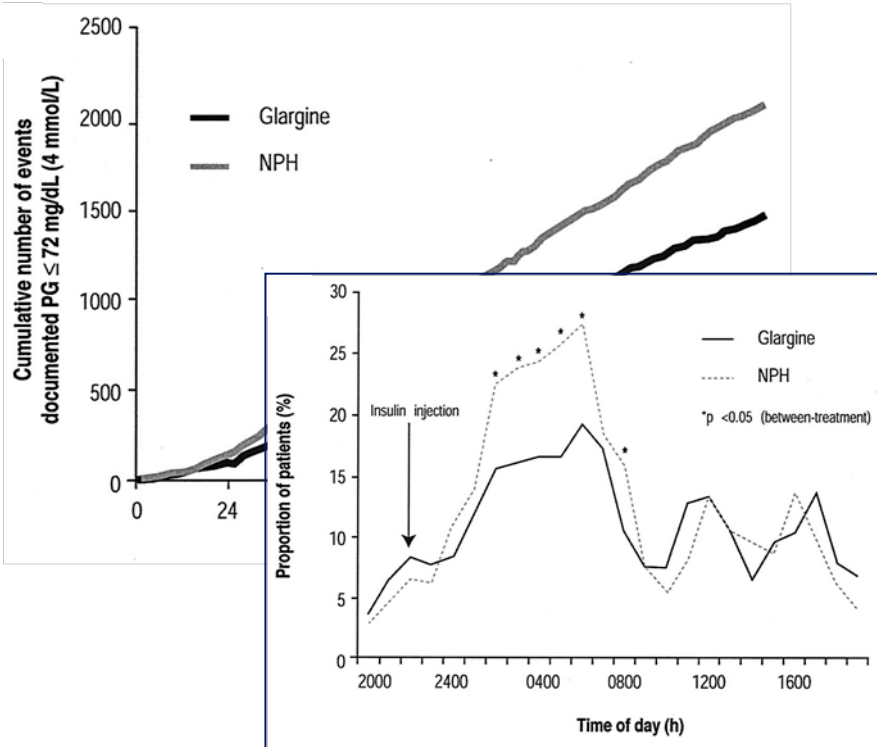
A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes

JULIO ROSENSTOCK, MD¹
GEORGE DAILEY, MD²
MASSIMO MASSI-BENEDETTI, MD³

ANDREAS FRITSCHKE, MD⁴
ZHENGNING LIN, PHD³
ALAN SALZMAN, MD³

Basalinsuline NPH Insulin vs. Insulin glargine (100IU/ml)

Reduktion von Unterzuckerungen (Hypoglykämien)



Basalinsuline Insulin glargine 300IU/ml vs 100IU/ml

original article

Diabetes, Obesity and Metabolism 17: 859–867, 2015.

© 2015 The Authors. *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes

R. Ritzel¹, R. Roussel^{2,3,4}, G. B. Bolli⁵, L. Vinet⁶, C. Brulle-Wohlhueter⁷, S. Glezer⁷ & H. Yki-Järvinen⁸

¹ *Klinikum Schwabing, Städtisches Klinikum München GmbH, Munich, Germany*

² *Diabetology Endocrinology Nutrition, DHU FIRE, Bichat Hospital, Assistance Publique Hôpitaux de Paris, Paris, France*

³ *INSERM U1138, Centre de Recherche des Cordeliers, Paris, France*

⁴ *UFR de Médecine, Université Paris Diderot, Sorbonne Paris Cité, Paris, France*

⁵ *Department of Medicine, University of Perugia, Perugia, Italy*

⁶ *EXPERIS IT, Nanterre, France*

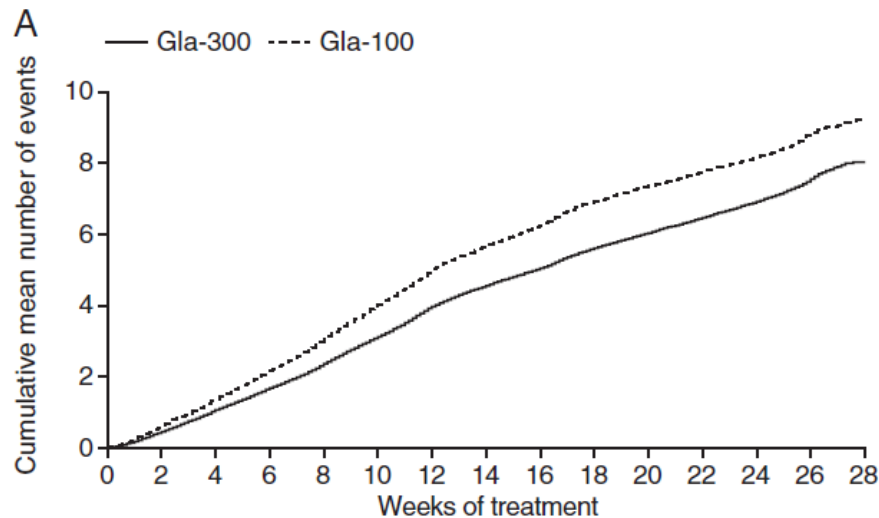
⁷ *Sanofi, Paris, France*

⁸ *Division of Diabetes, Faculty of Medicine and Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland*

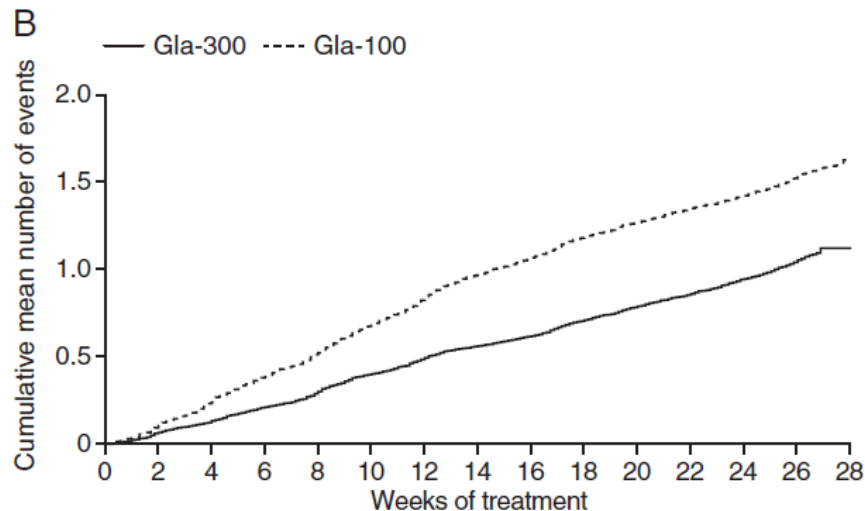
Basalinsuline Insulin glargine 300IU/ml vs 100IU/ml

Cumulative mean number of confirmed [≤ 3.9 mmol/l (≤ 70 mg/dl)] or severe hypoglycaemic events for pooled analysis of all three studies (EDITION 1,2,3)

Any time of day (24 h)

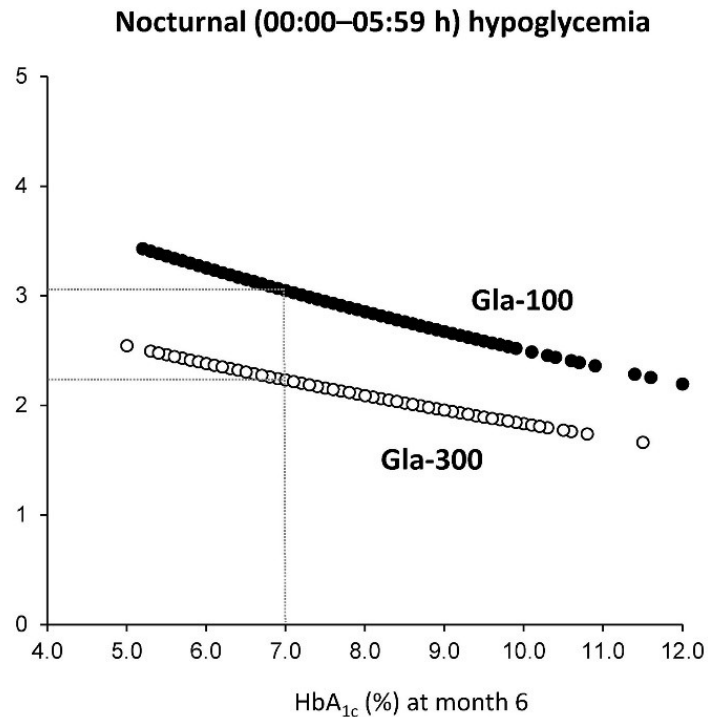
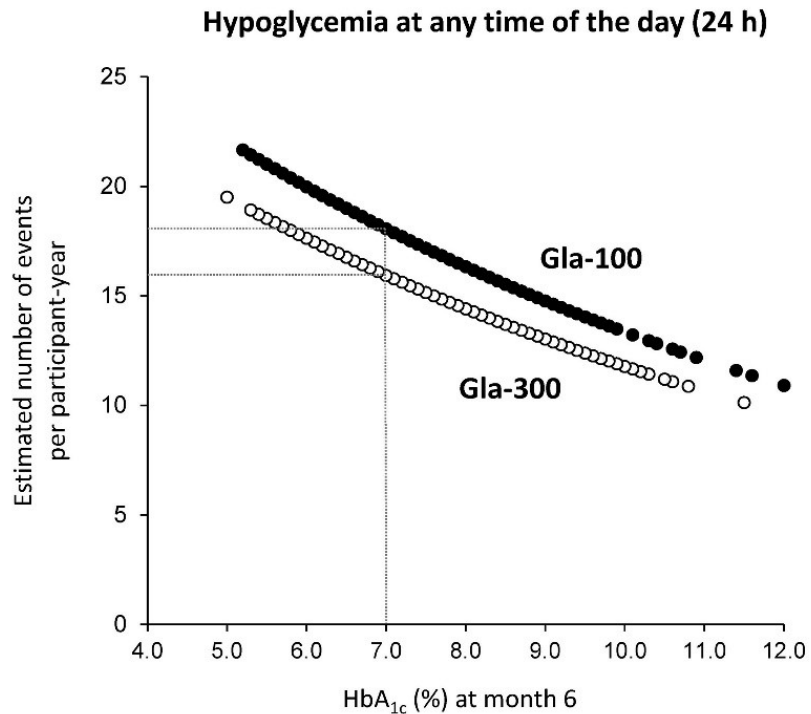


Nocturnal (00:00–05:59 h)

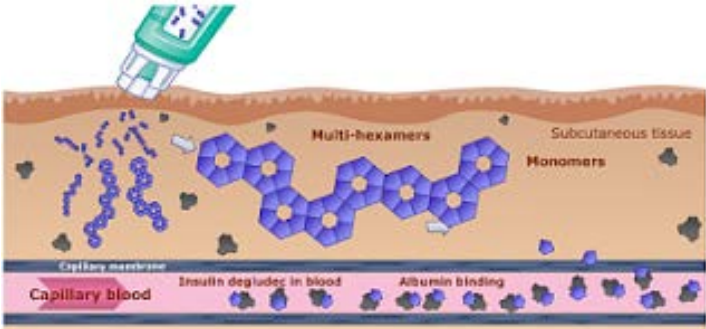
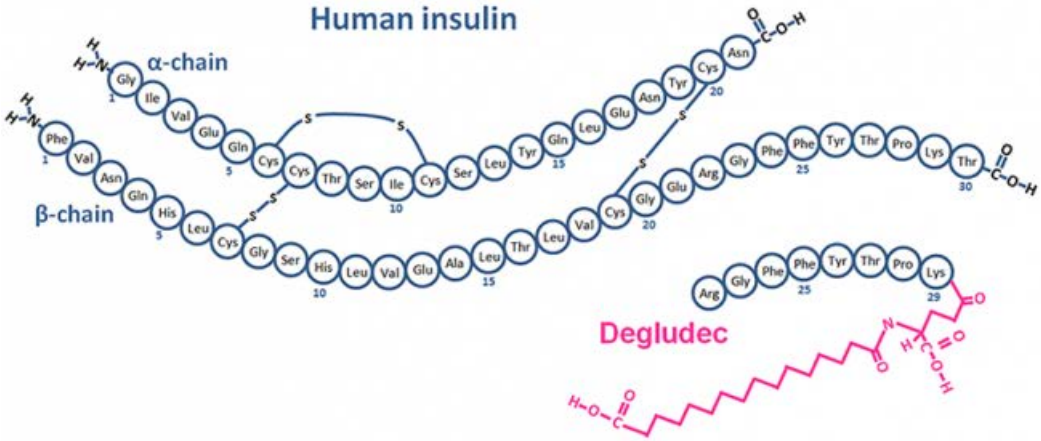


Gla-100, insulin glargine 100 IU/ml; Gla-300, insulin glargine 300 IU/ml.

Basalinsuline Insulin glargine 300U/I vs 100U/I

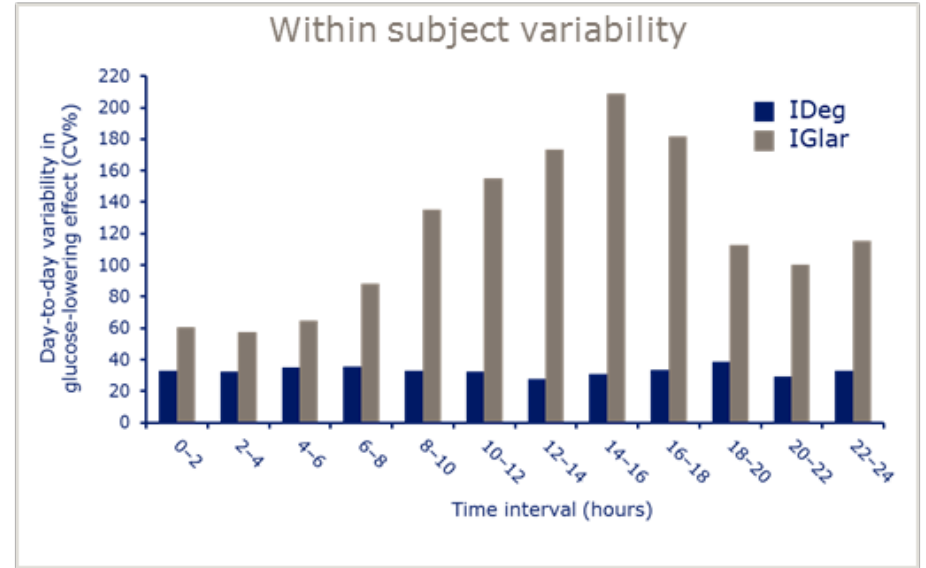
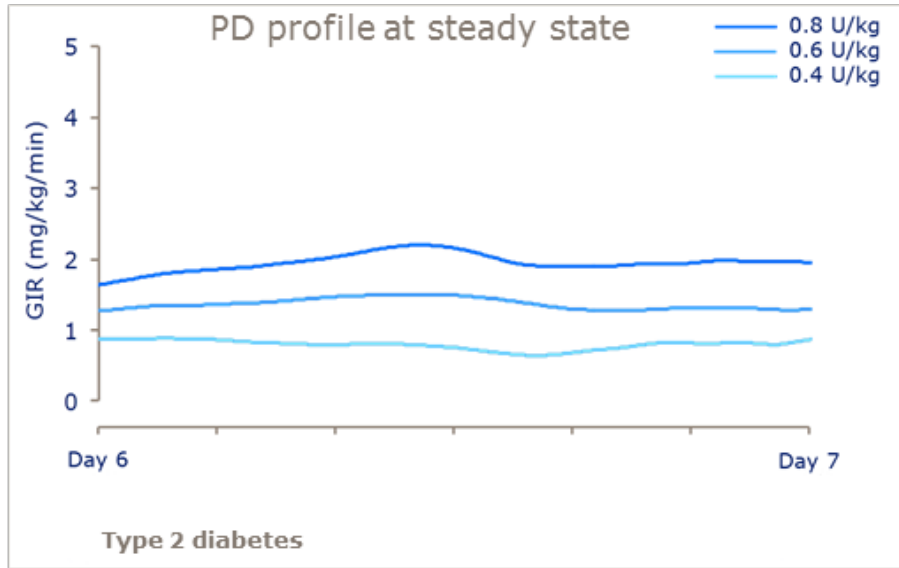


Basalinsuline Insulin degludec



Basalinsuline

Insulin glargine (100IU/ml) vs Insulin degludec



Within-subject variability: Heise T et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes. Metab.* 2012 Sep;14(9):859-64.

Pharmacodynamic profile at steady state: Heise et al. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. *Diabetes Obes. Metab.* 2012 Oct;14(10):944-50.

GIR: Glucose infusion rate i.e. glucose lowering effect; IDeg: insulin degludec; IGlar: insulin glargine; PD: pharmacodynamic

Basalinsuline

Insulin glargine (100IU/ml) vs Insulin degludec

original article

Diabetes, Obesity and Metabolism 15: 175–184, 2013.
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Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials

R. E. Ratner¹, S. C. L. Gough², C. Mathieu³, S. Del Prato⁴, B. Bode⁵, H. Mersebach⁶, L. Endahl⁶ & B. Zinman⁷

¹Division of Endocrinology, Department of Medicine, Georgetown University School of Medicine, Washington, DC, USA

²Oxford Centre for Diabetes, Endocrinology and Metabolism and NIHR Oxford Biomedical Research Centre, Oxford, UK

³University Hospitals (UZ) Leuven, KU Leuven, Leuven, Belgium

⁴University of Pisa, Pisa, Italy

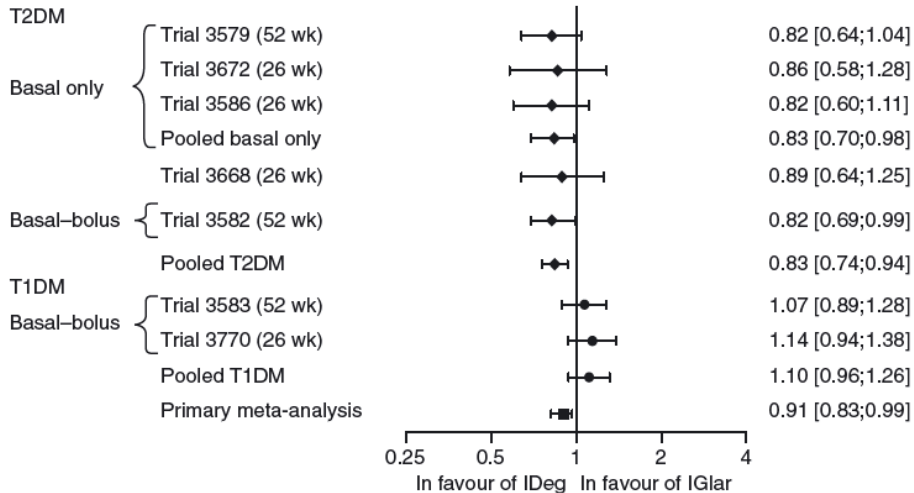
⁵Atlanta Diabetes Associates, Atlanta, GA, USA

⁶Novo Nordisk, Søborg, Denmark

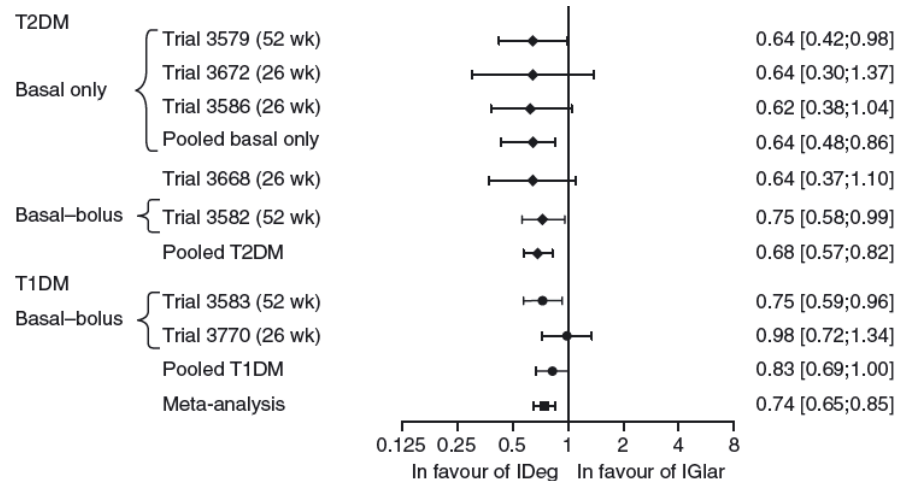
⁷University of Toronto, Mount Sinai Hospital, Toronto, ON, Canada

Basalinsuline

Insulin glargine (100IU/ml) vs Insulin degludec



overall confirmed hypoglycaemic episodes



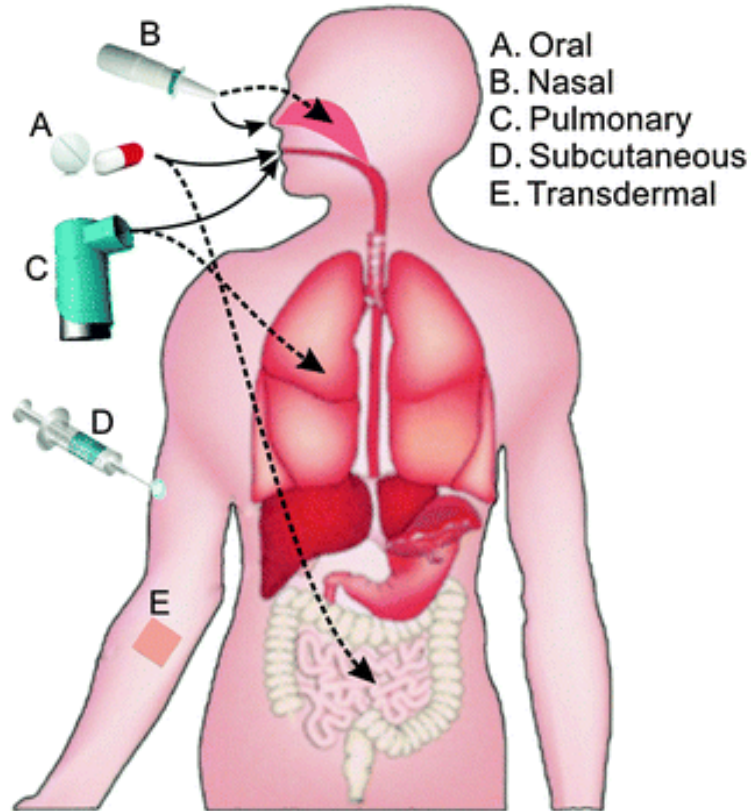
Innovationen in der Insulinentwicklung

Summary (1)



- ▶ Insulinentwicklung folgt ungelösten medizinischen (therapeutischen) Bedürfnissen
- ▶ Physiologisch unterscheiden wir sehr schnelle Insulinabgabe (Sekunden) bei Mahlzeiten und konstante, gleichmäßige Insulinabgabe für den Grundstoffwechsel
- ▶ Die subkutane Insulininjektion ist eine Herausforderung für die schnelle Insulinwirkung (Mahlzeiten) und lange, gleichmäßige Insulinwirkung (Grundumsatz)
- ▶ Insulinentwicklungen, Veränderung des Insulinmoleküls, Anhang von langkettigen Molekülen, Veränderungen der pharmakologischen Formulierung, etc., verbessern Schnelligkeit und lange, gleichmäßige Wirkung und zeigen in klinischen Studien Vorteile in Wirkung und Sicherheit

Innovationen in der Insulinentwicklung



Innovationen in der Insulinentwicklung

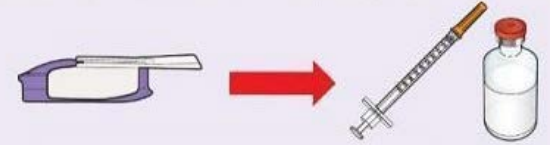
Inhalatives (Human-) Insulin



EXUBERA
insulin human [rDNA origin]
Inhalation Powder



To switch from AFREZZA® to injected mealtime insulin...

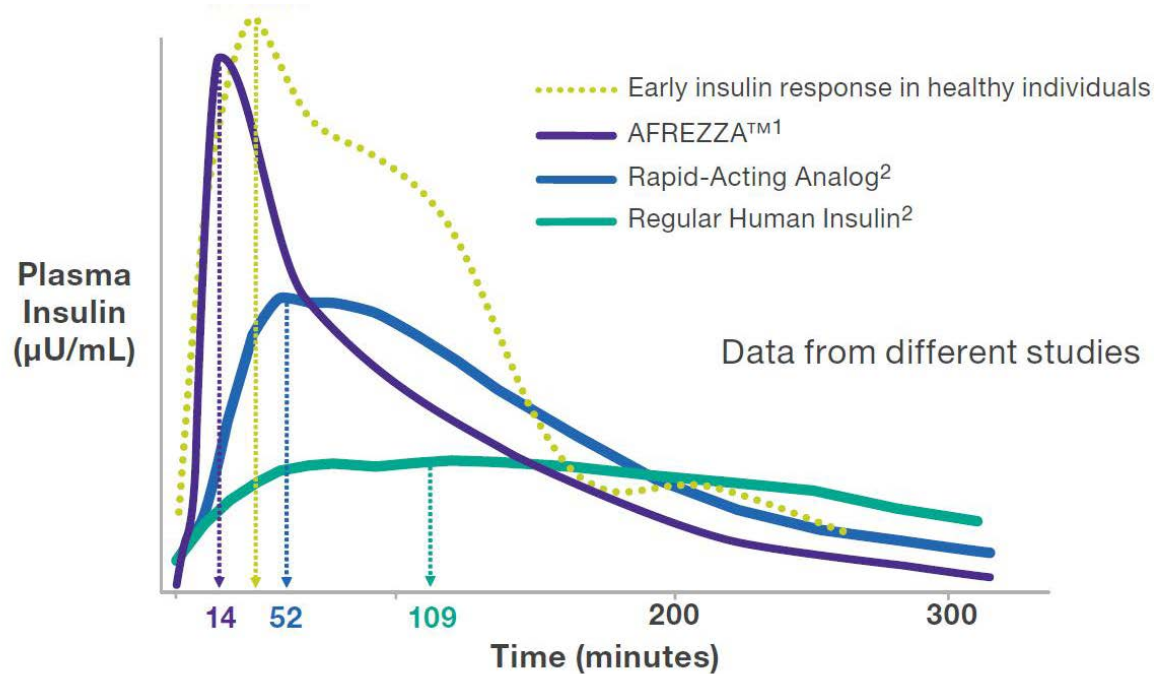


Find your AFREZZA® dose in the chart.

AFREZZA® Dose	# of 4 unit (blue) cartridges needed	# of 8 unit (green) cartridges needed	Injected Mealtime Insulin Dose
4 units	1		4 units
8 units		1	8 units
12 units	1 +	1	12 units
16 units		2	16 units
20 units	1 +	2	20 units
24 units		3	24 units

Innovationen in der Insulinentwicklung

Inhalatives (Human-) Insulin

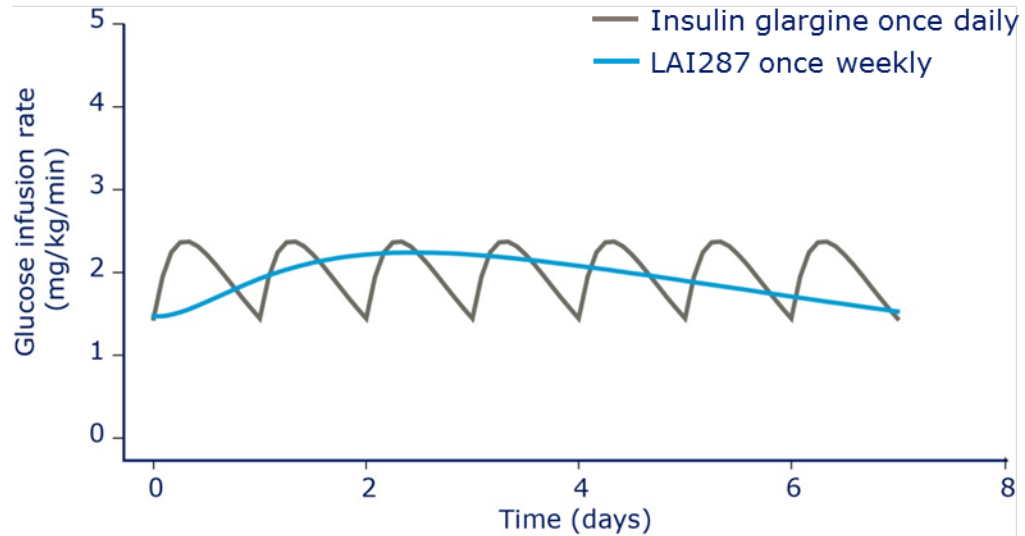
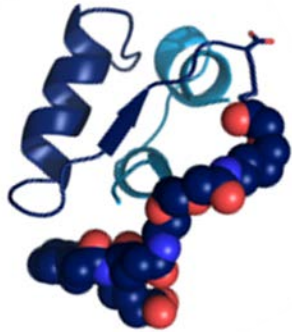


1. Non-diabetic obese subjects after 100 g oral glucose. Adapted from Kipnis D. *Ann Intern Med.* 1968;69:891-900.

2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. *Diabetes Care.* 1999;22:1501-1506.

Innovationen in der Insulinentwicklung

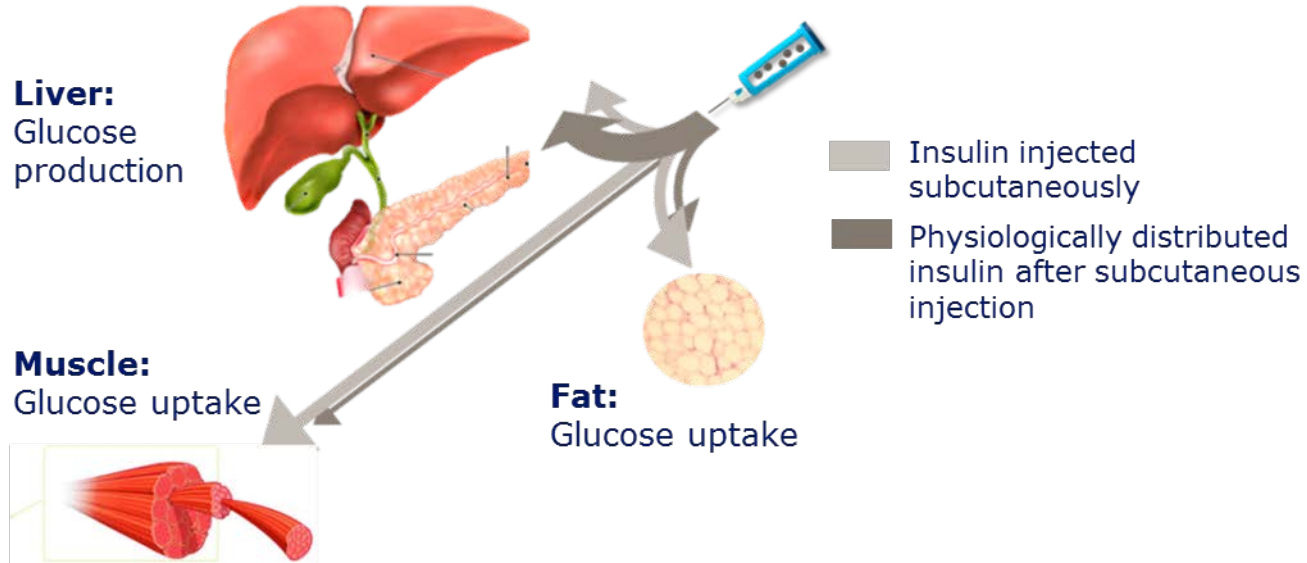
Super lang-wirksame Basalinsuline



Innovationen in der Insulinentwicklung

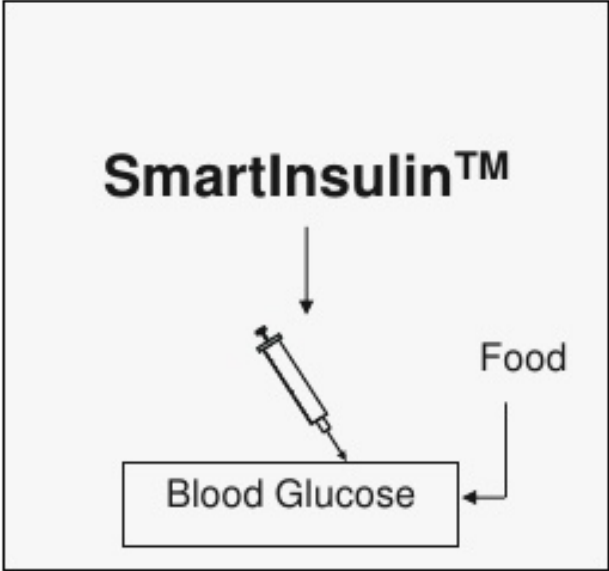
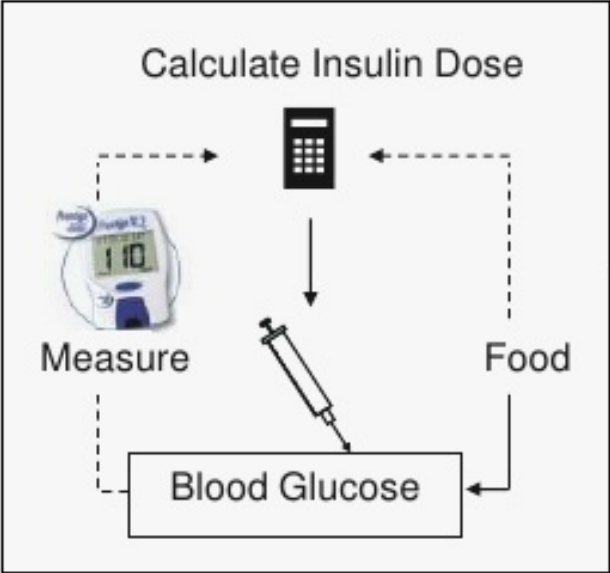
"Liver preferential" Mahlzeiteninsulin

Mimicking physiology



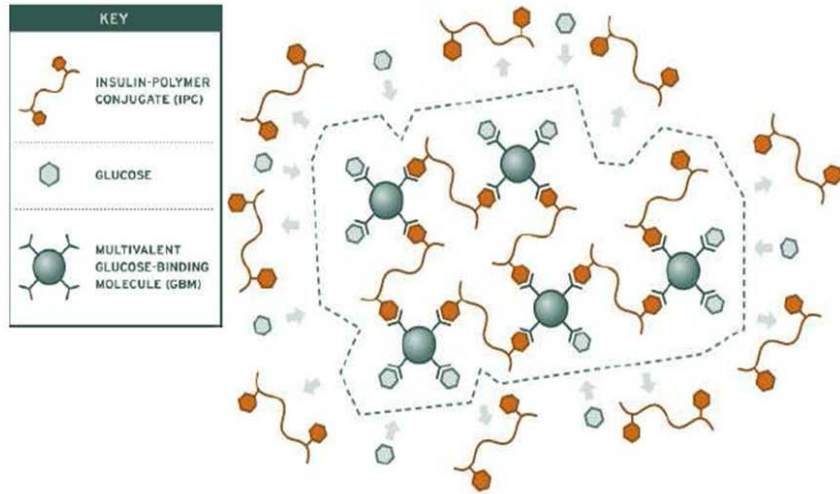
Innovationen in der Insulinentwicklung

Smart Insulin



Innovationen in der Insulinentwicklung

Smart Insulin

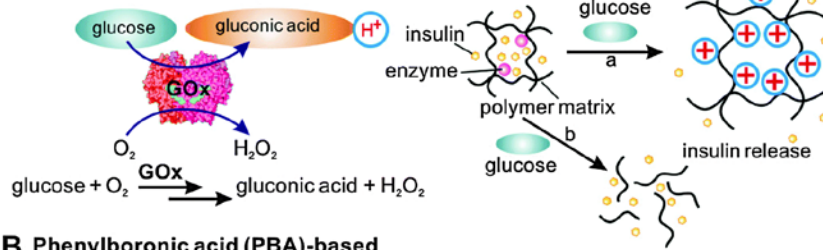


- ▶ *Smart Insulin™ consists of a layered, biocompatible and biodegradable polymer-therapeutic that is bound to an engineered glucose-binding molecule.*
- ▶ *Insulin is released from Smart Insulin only when the polymer-therapeutic is unbound from Insulin by the presence of a specific glucose concentration.*

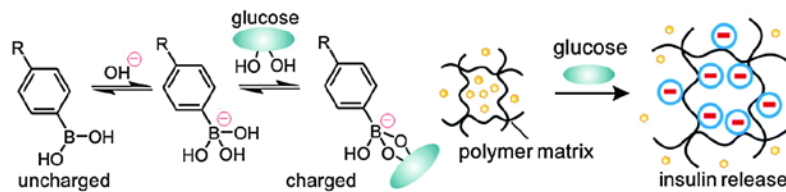
Innovationen in der Insulinentwicklung

Smart Insulin

A Glucose-specific enzyme-based



B Phenylboronic acid (PBA)-based



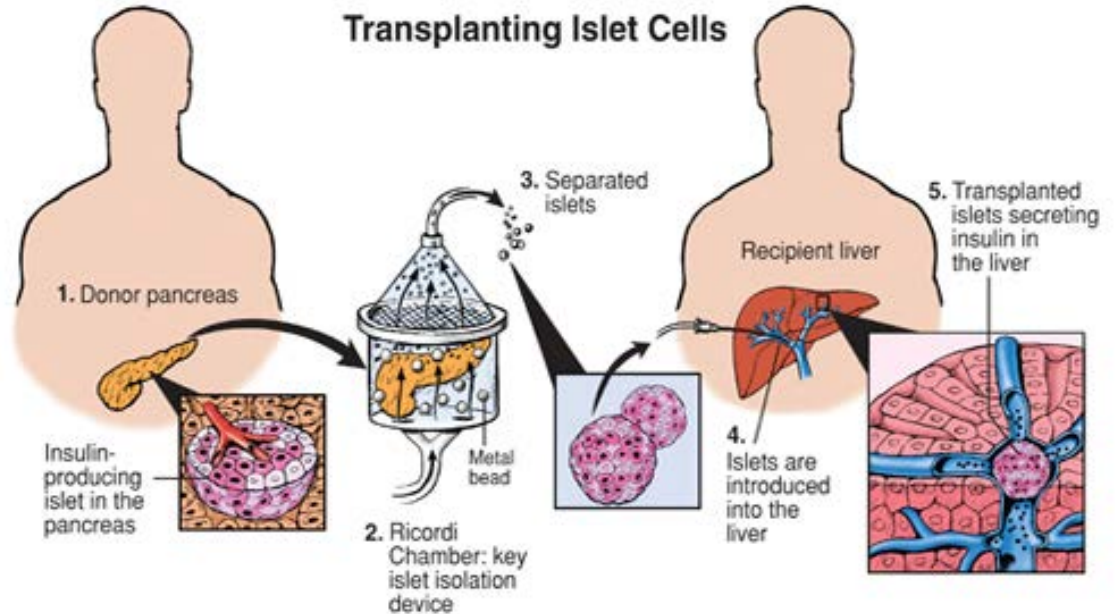
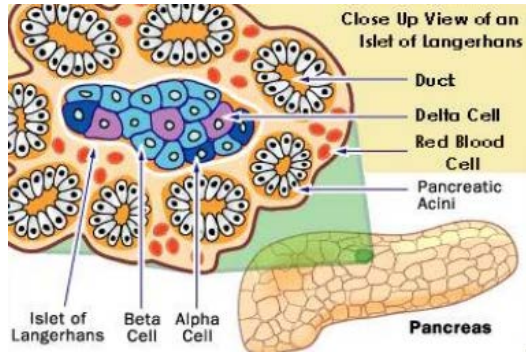
C Glucose binding protein (GBP)-based



- *Schematic illustration of the mechanism of the classic synthetic closed-loop insulin delivery systems*

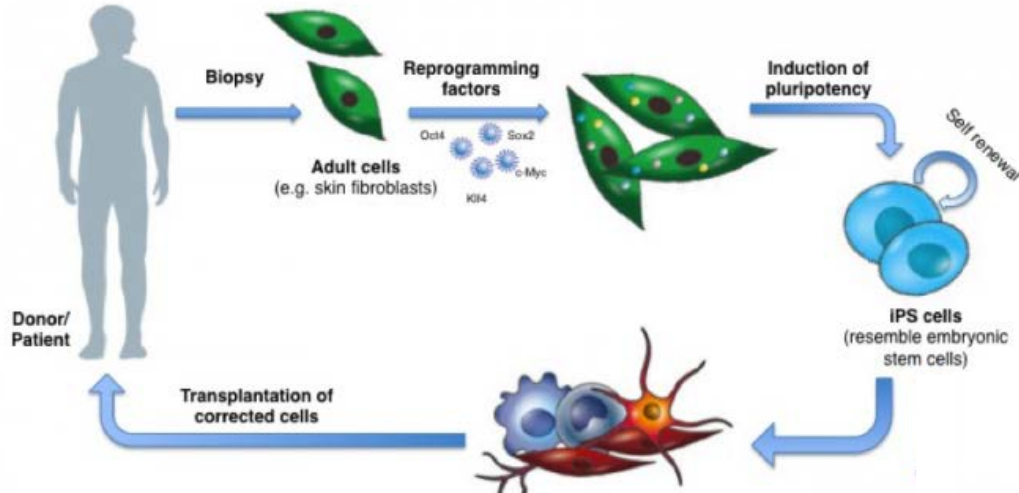
Innovationen in der Insulinentwicklung

Inselzelltransplantation

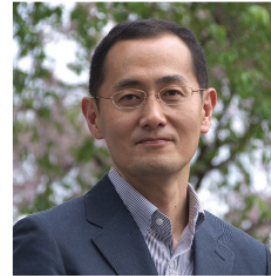


Innovationen in der Insulinentwicklung

Produktion von Inselzellen der Bauchspeicheldrüse durch "induced pluripotent stem cells" Methode



2012 Nobel Prize in Physiology or Medicine



Shinya Yamanaka
University of Kyoto, Japan
Photo Credit:
Center for iPS cell Research and Application, Kyoto University



John B. Gurdon
Gurdon Institute in Cambridge, UK

Innovationen in der Insulinentwicklung

Summary (2)



- ▶ Insulinentwicklung folgt ungelösten medizinischen (therapeutischen) Bedürfnissen
- ▶ Bedürfnisse sind
 - schneller (*bessere Wirksamkeit und Flexibilität*)
 - länger (*sicherer, Reduktion der Injektionshäufigkeit*)
 - andere Applikationsweg
(*keine Injektionen, Wirkung und Sicherheit*)
 - Leberspezifität (*bessere Wirksamkeit, Sicherheit*)
 - automatische Insulinwirkung
(*keine Blutzuckermessung, Wirksamkeit und Sicherheit*)
 - Ersatz der zerstörten Inselzellen
 - etc.etc.etc.
- ▶ Solange die Insulintherapie in Ihrer Wirksamkeit durch potentiell lebensbedrohliche Komplikationen bedroht bzw. eingeschränkt ist muss Insulforschung und -Entwicklung weitergehen

Typ 2 Diabetes

Type 2 diabetes

gestational diabetes



Caused by insulin resistance and relative deficiency, where insulin produced by the body is not used effectively.³



Almost half of all people with type 2 diabetes are not aware that they have it⁴

Type 2 diabetes accounts for 85%-95% of all diabetes in high-income countries⁵

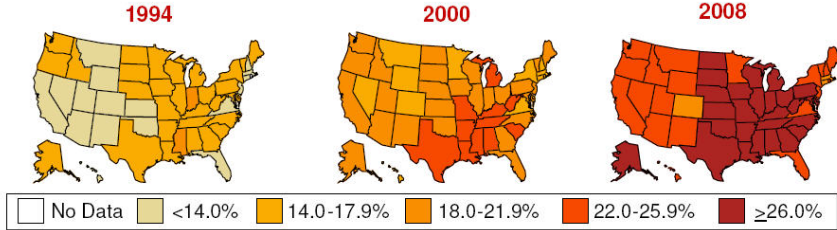
80%

of type 2 diabetes cases are believed to be preventable by changing diet and levels of physical activity⁶

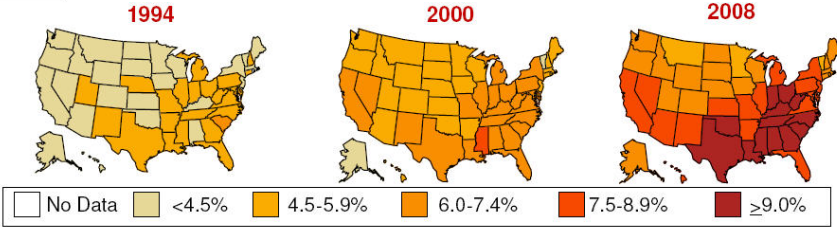


Behandlung der Pandemie des Typ 2 Diabetes

Obesity (BMI ≥ 30 kg/m²)



Diabetes

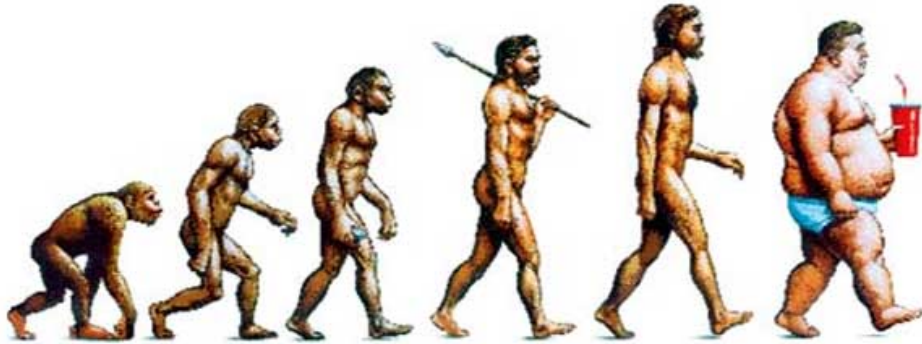


CDC's Division of Diabetes Translation, National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



Behandlung des Typ 2 Diabetes

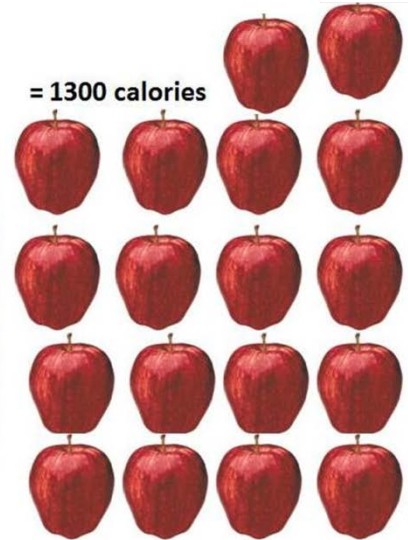
Lebensstiländerung + medikamentöse Therapie (auch Insulin) mit unterschiedlichen Ansätzen



= 1300 calories



= 1300 calories

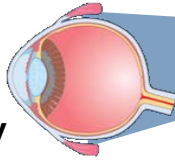


Typ 2 Diabetes ... was passiert ohne Therapie ?



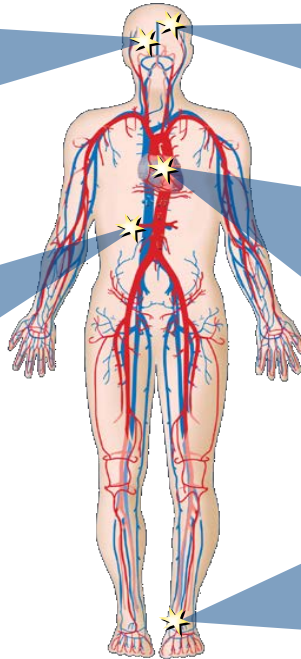
Diabetic Retinopathy

Leading cause of blindness in adults^{1,2}



Diabetic Nephropathy

Leading cause of end-stage renal disease^{3,4}



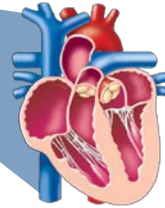
Stroke

2- to 4-fold increase in cardiovascular mortality and stroke⁵



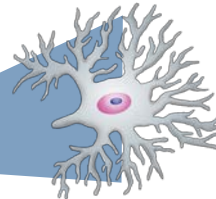
Cardiovascular Disease

8/10 individuals with diabetes die from CV events⁶



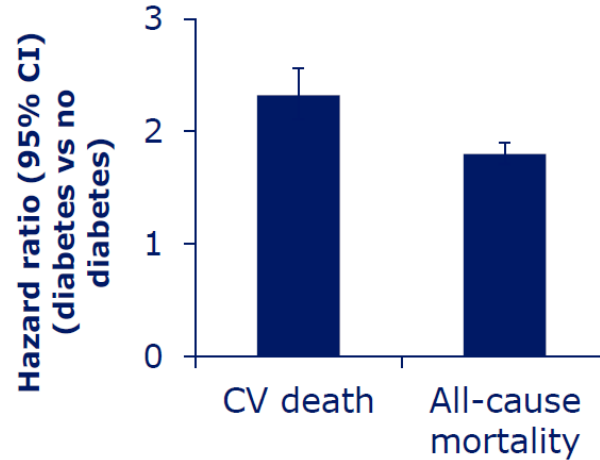
Diabetic Neuropathy

Leading cause of non-traumatic lower extremity amputations^{7,8}



Innovationen in der Behandlung des Typ 2 Diabetes müssen auch das Komplikationsrisiko senken

Mortality risk associated with diabetes (n=820,900)¹



1. Seshasai et al. N Engl J Med 2011;364:829-41;

2. Centers for Disease Control and Prevention National Diabetes Fact Sheet 2011. <http://www.cdc.gov/diabetes>;

3. IDF diabetes atlas 7th edition. 2015. Available at: <http://www.diabetesatlas.org/>

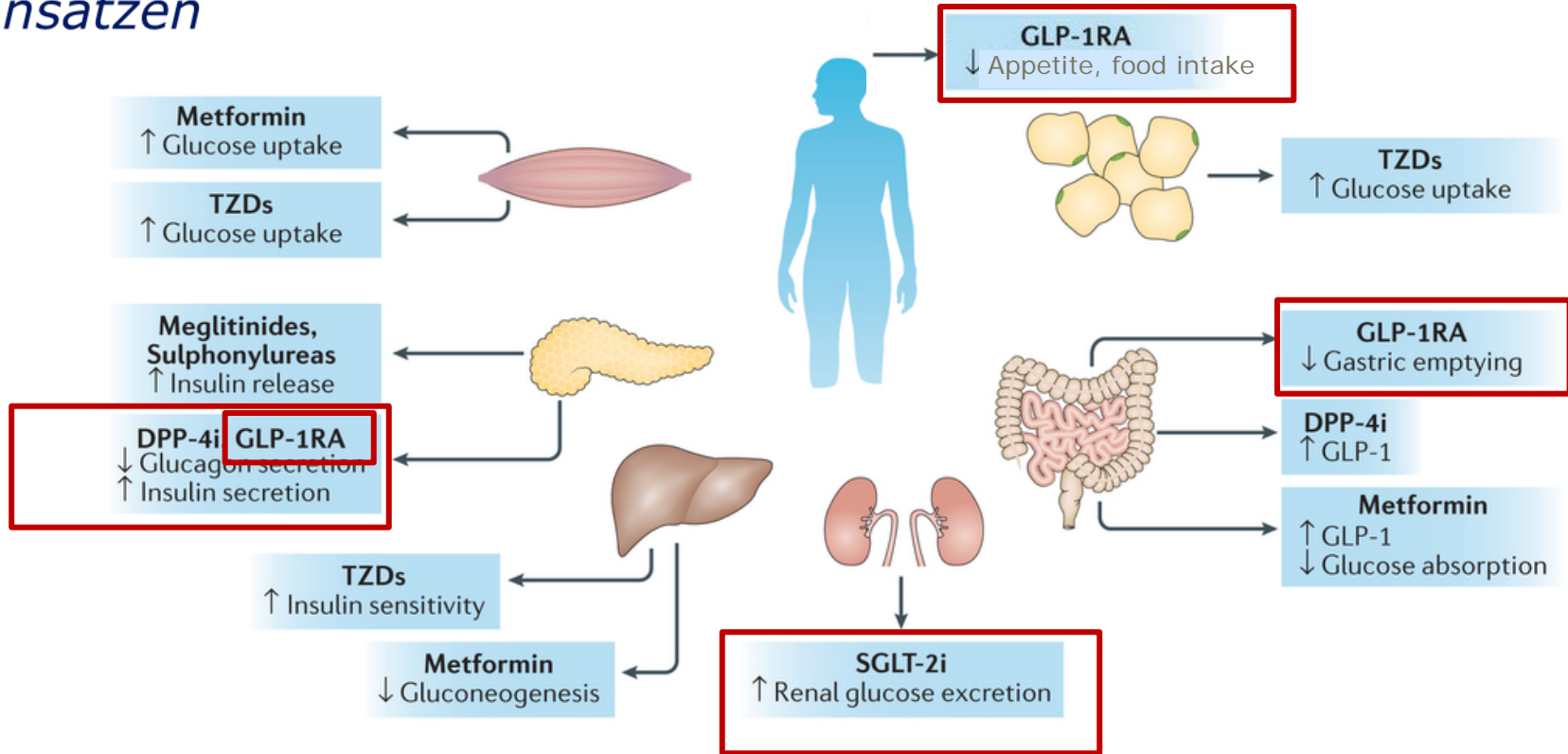
4. UKPDS, NEJM. 2008;359(15):1577-89

5. Heart Outcomes Prevention Evaluation (HOPE) Study, The lancet, 2000, 355: 253-59.

6. Heart Protection Study, Lancet 2003: 361: 2005-16

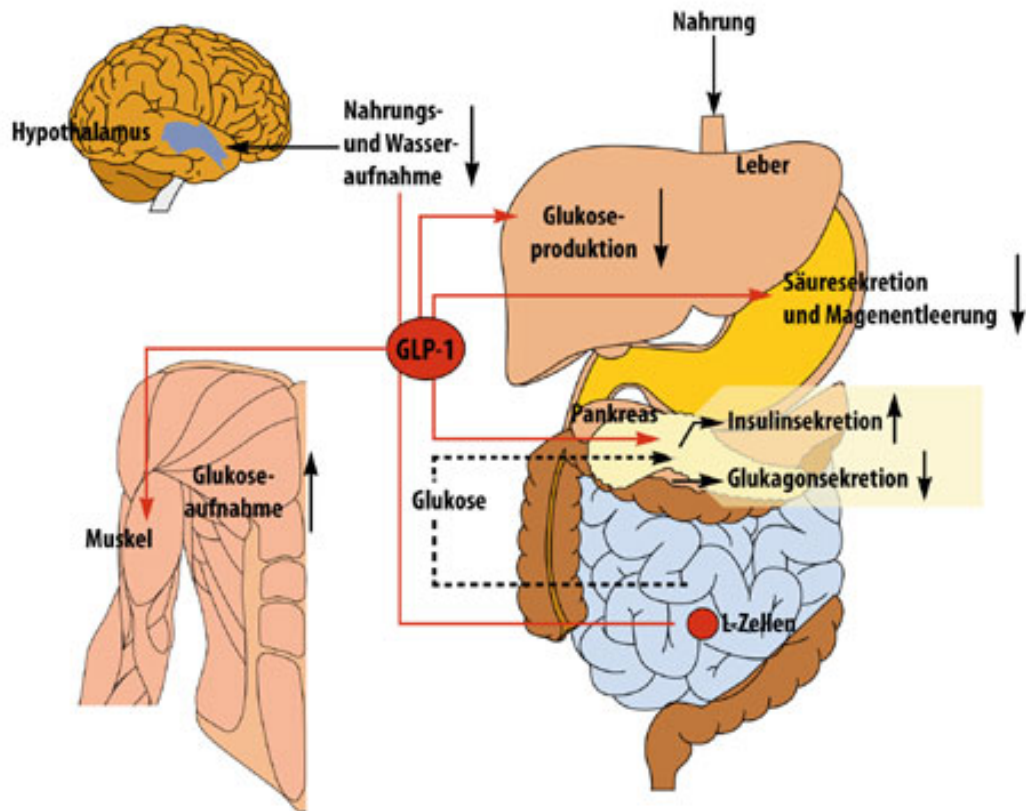
Behandlung des Typ 2 Diabetes

Medikamentöse Therapie (auch Insulin) mit unterschiedlichen Ansätzen



Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten



Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten **Gewichtsabnahme**

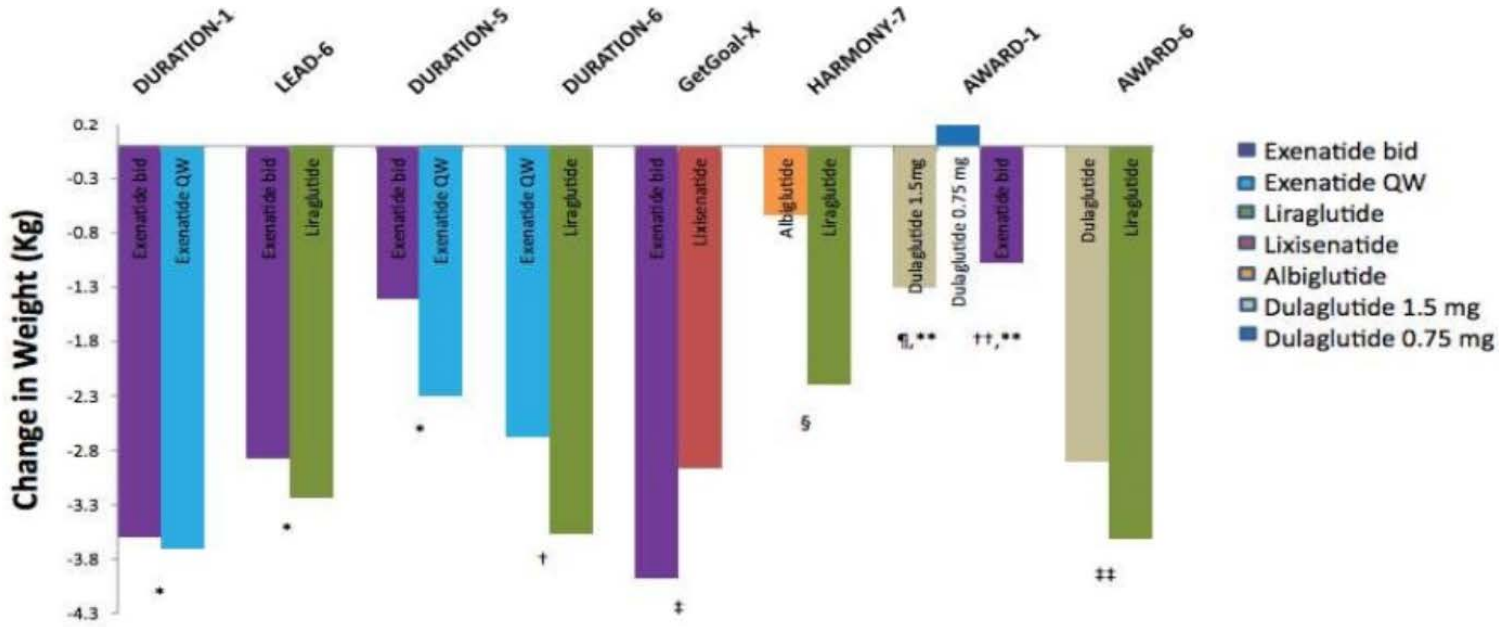


Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority (unless noted for noninferiority); **p*=not significant, †*p*=0.0005, ‡*p*-value not reported for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), §*p*<0.0001, ¶ *p*<0.001 versus dulaglutide 0.75 mg, ***p*=not significant between dulaglutide 1.5 mg versus exenatide bid, ††*p*=0.011.

Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten

LEADER

Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

ESTABLISHED IN 1812

JULY 28, 2016

VOL. 375 NO. 4

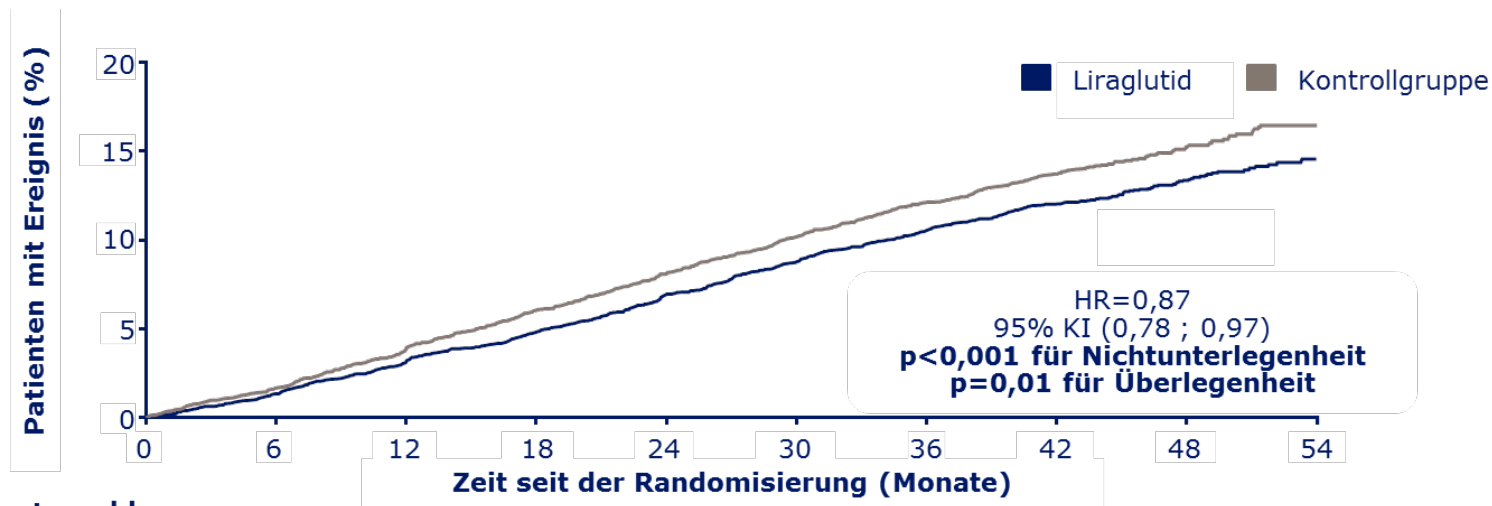
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A.,
Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D.,
Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D.,
Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten

Liraglutide senkt die Sterblichkeit an Herz- / Kreislaufkrankungen in Risikopatienten mit Typ2 Diabetes



Patientenzahl

Liraglutid	4.668	4.593	4.496	4.400	4.280	4.172	4.072	3.982	1.562	424
Kontrollgruppe	4.672	4.588	4.473	4.352	4.237	4.123	4.010	3.914	1.543	407

Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten

SUSTAIN-6

SEMAGLUTIDE UNABATED SUSTAINABILITY
IN TREATMENT OF TYPE 2 DIABETES

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

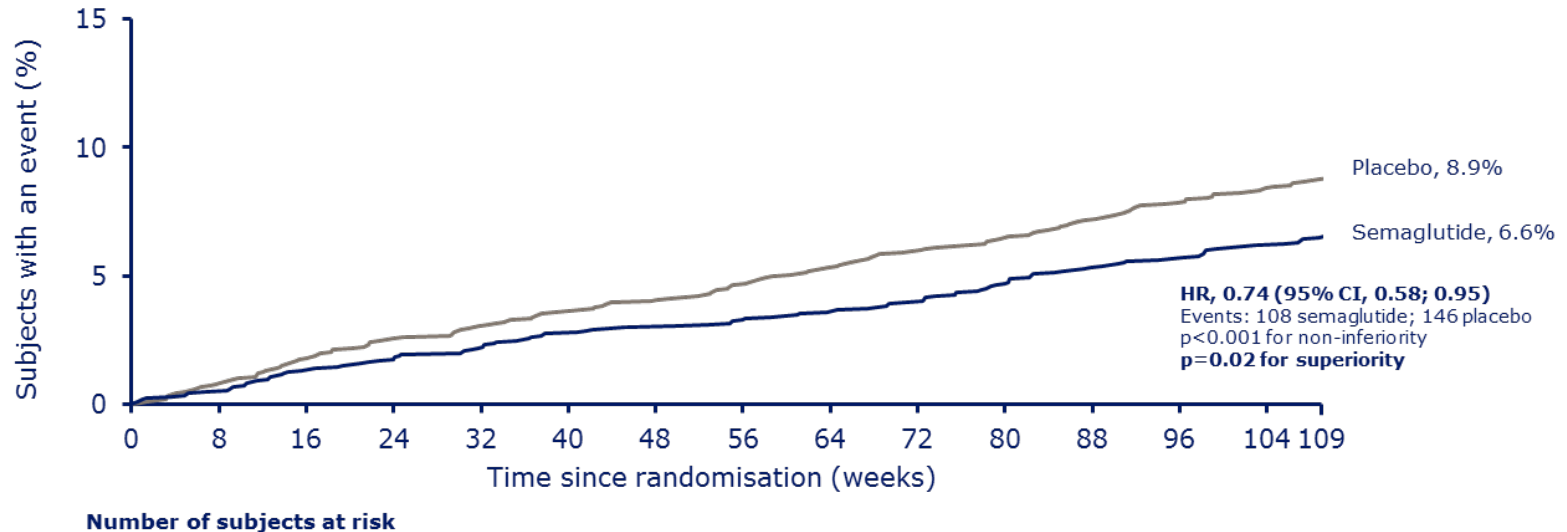
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D.,
Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D.,
Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D.,
Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D.,
Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D.,
and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

N ENGL J MED 375;19 NEJM.ORG NOVEMBER 10, 2016

Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten

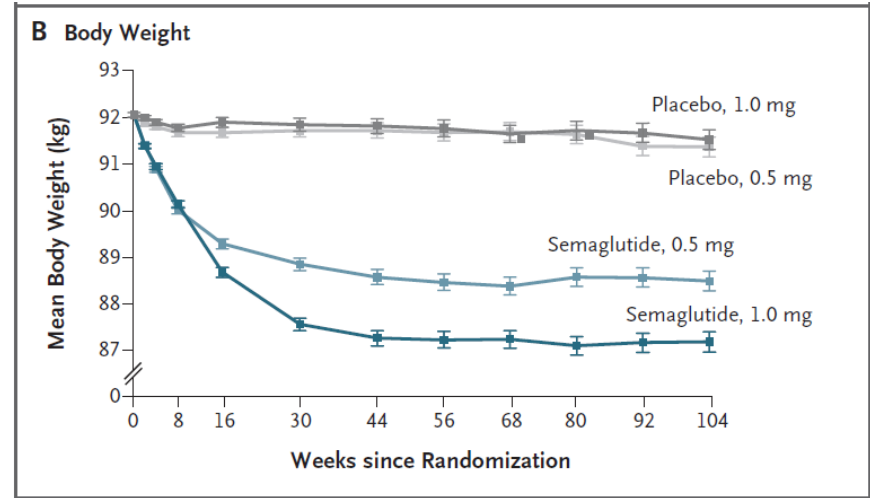
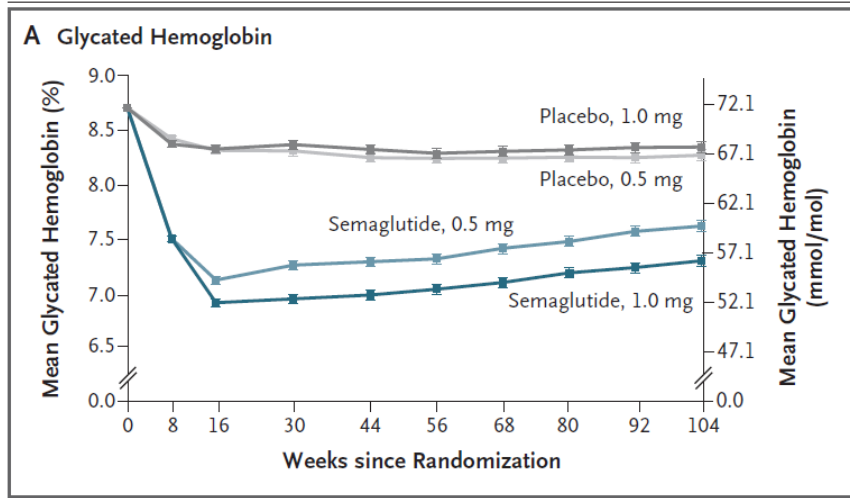
Semaglutide senkt die Sterblichkeit an Herz- / Kreislauferkrankungen in Risikopatienten mit Typ2 Diabetes



Innovationen in der Behandlung des Typ 2 Diabetes

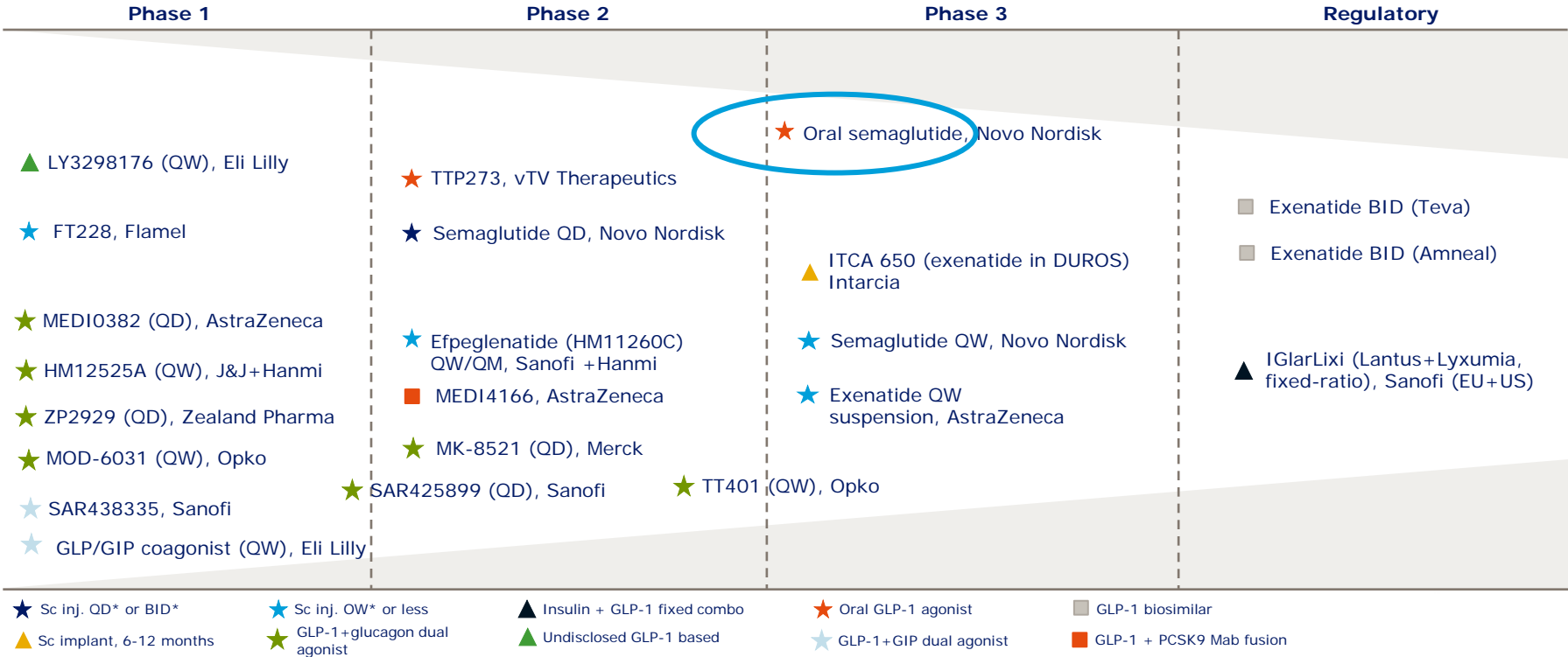
GLP-1 Rezeptoragonisten

Semaglutide senkt Blutzucker (HbA1c) und Gewicht



Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten Pipeline



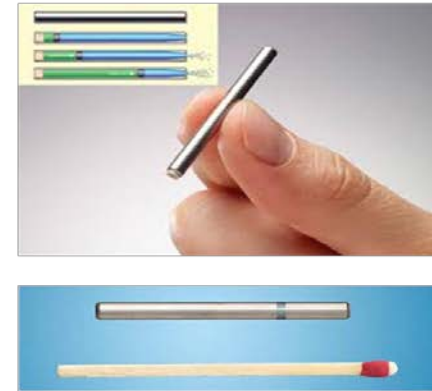
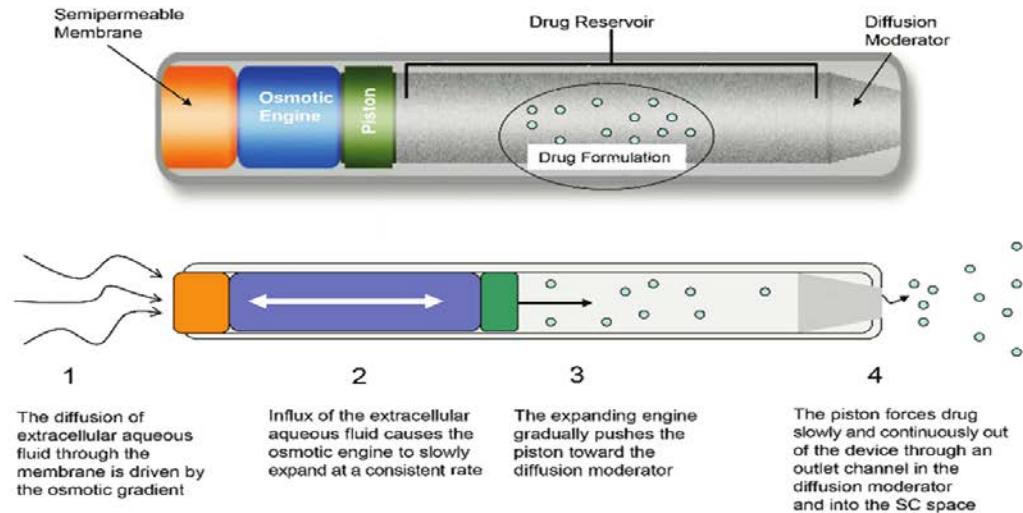
*QD: Once a day (quaque die); BID: Twice a day (bis in die); QW: Once weekly; QM: Once monthly.

Innovationen in der Behandlung des Typ 2 Diabetes

GLP-1 Rezeptoragonisten *Pipeline*

Intarcia's exenatide mini-pump ITCA-650

6-12 Monate Behandlung mit einem implantierbaren Device "minipump"



Nicht alle GLP-1 Rezeptoragonisten sind gleich ... und haben eine Reduktion des CV Risikos gezeigt

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
N	16.500	14.000	21.000	14000	9622
Results	BENEFICIAL	NEUTRAL	BENEFICIAL	2018	2019

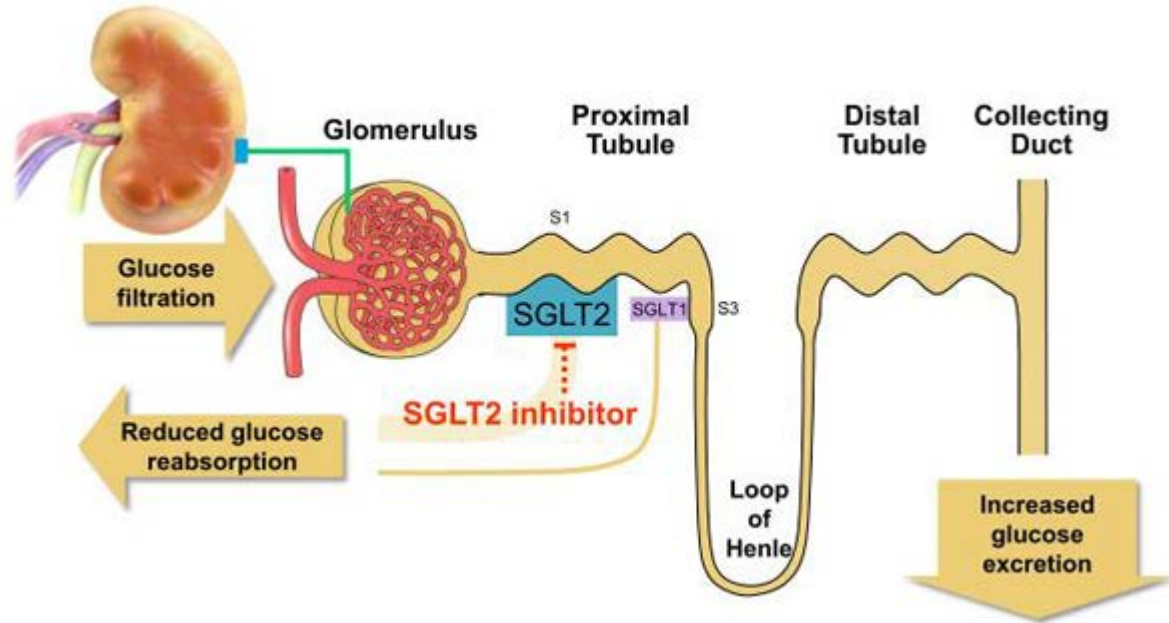
Cardiovascular Outcomes With Antihyperglycemic Therapy: Past, Present, and Future Impact on Practice

Authors: Carol H. Wysham, MD; John E. Anderson, MD; Lawrence Blonde, MD; Serge A. Jabbour, MD; Faculty and Disclosures

CME Released: 6/23/2016

Innovationen in der Behandlung des Typ 2 Diabetes

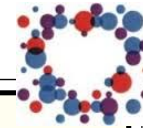
SGLT-2 Inhibitoren



Innovationen in der Behandlung des Typ 2 Diabetes

SGLT-2 Inhibitoren

The NEW ENGLAND JOURNAL of MEDICINE



EMPA-REG
OUTCOME

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

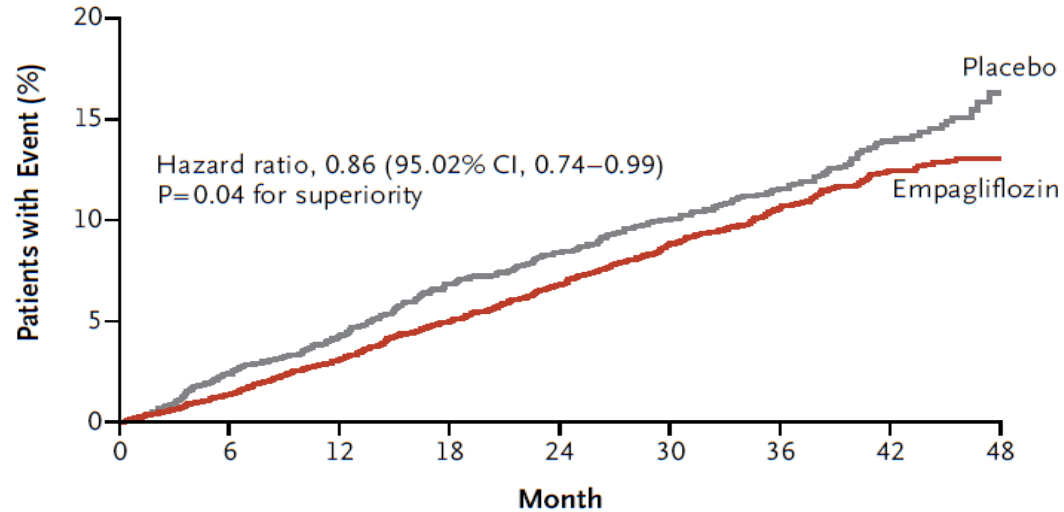
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,
Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H.,
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D.,
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

Innovationen in der Behandlung des Typ 2 Diabetes

SGLT-2 Inhibitoren

Primary Outcome



No. at Risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Innovationen in der medikamentösen Behandlung von Typ 2 Diabetes

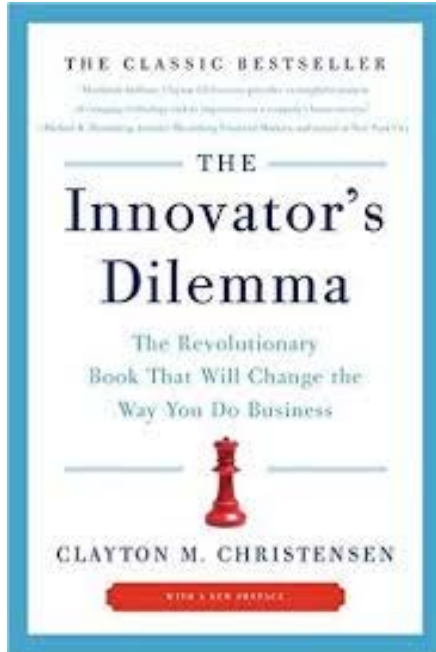
Summary (3)



- ▶ Medikamentöse Therapie des Typ 2 Diabetes benutzt unterschiedliche Wirkmechanismen und Zielorgane um Blutzucker zu normalisieren
- ▶ Moderne Diabetesmedikamente normalisieren nicht nur Blutzucker ohne die Gefahr von Hypoglykämien sondern reduzieren Körpergewicht, und adressieren weitere metabolische Zielparameter, z.B. RR, Lipidstoffwechsel, etc.
- ▶ Die GLP-1 Rezeptoragonisten Liraglutide und Semaglutide und der SGLT-2 Inhibitor Empagliflozin haben in großen kardiovaskulären (CV) Outcome Studien gezeigt, dass sie in Typ 2 Patienten mit hohem CV Risiko die CV Sterblichkeit signifikant reduzieren
- ▶ Damit ist der Behandlungsstandard für Typ 2 Diabetes und das Ziel für kommende Innovationen nicht mehr ausschließlich auf die Normalisierung des BZ ausgerichtet sondern auf die Senkung von Komplikationen und Sterblichkeit

Innovationen lösen unmet medical needs

Evolutionär oder disruptiv



--- **evolutionäre Innovation**

bestehende Technologien oder existierende Produkt werden verbessert, effizienter oder günstiger.

--- **disruptive Innovation**

verändert die Spielregeln auf dem Markt oder im Nutzungsverhalten.

Innovationen in der Insulinentwicklung

disruptive ?

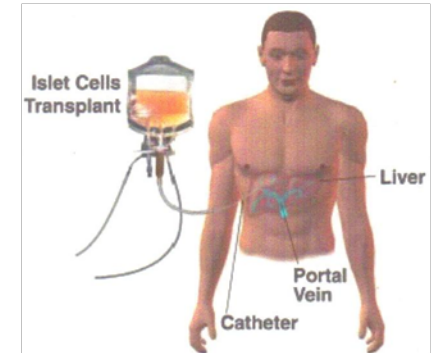
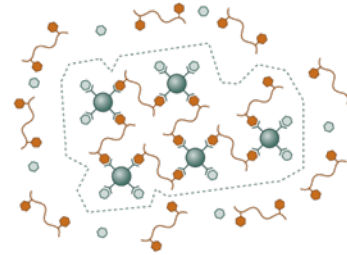
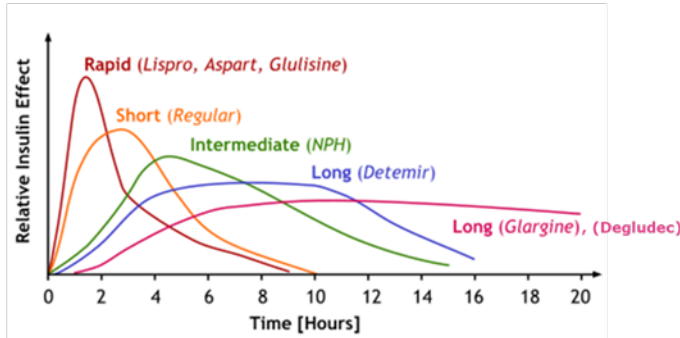
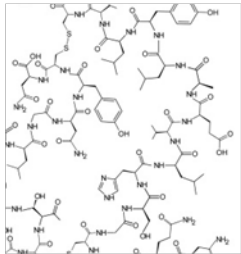
disruptive ?

Humaninsulin

Insulinanaloga

Smart Insulin

eigenes Insulin
Inselzelltransplantation



evolutionär

Innovationen in der Behandlung des Diabetes Mellitus

urin glucose test



1941 - Clinitest



blood glucose test - spot



1974 - Reflomat



continuous glucose monitoring



1999 - Sof-sensor®

CGM



CGM

(continuous monitoring)



real-time CGM

(continuous monitoring)



real-time CGM, implantable

(continuous monitoring)



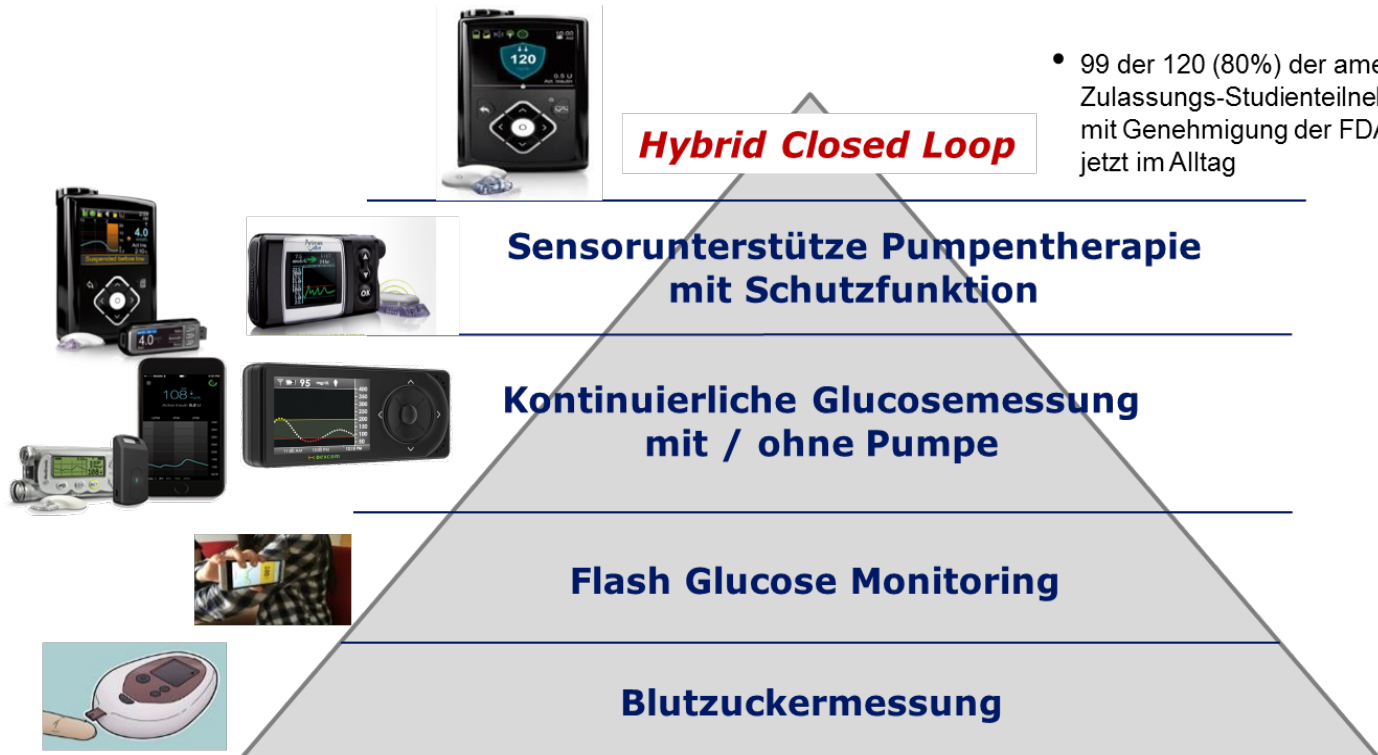
real-time CGM, non-invasive & others

(continuous monitoring)



Innovationen in der Behandlung des Diabetes Mellitus

Automatisierung der Insulintherapie = Closed Loop



- 99 der 120 (80%) der amerikanischen Zulassungs-Studienteilnehmer nutzen mit Genehmigung der FDA den HCL jetzt im Alltag


Innovationen sind wichtig für den Fortschritt in der Behandlung des Diabetes Mellitus und für den Pharma (wirtschafts) Standort Deutschland

Investments in GERMANY:



90 Novo Nordisk trials were conducted in Germany including **4,424** patients from 2012-2016²

51 million EUR Novo Nordisk R&D investments in Germany from 2012-2016²

74%  of health care professionals have diagnosed one or more diabetes complications during trial screenings³

75% of health care professionals believe that clinical trials contribute to overall improvements in treatment and patient care at their hospital/clinic³

Vielen Dank für
Ihre Aufmerksamkeit

